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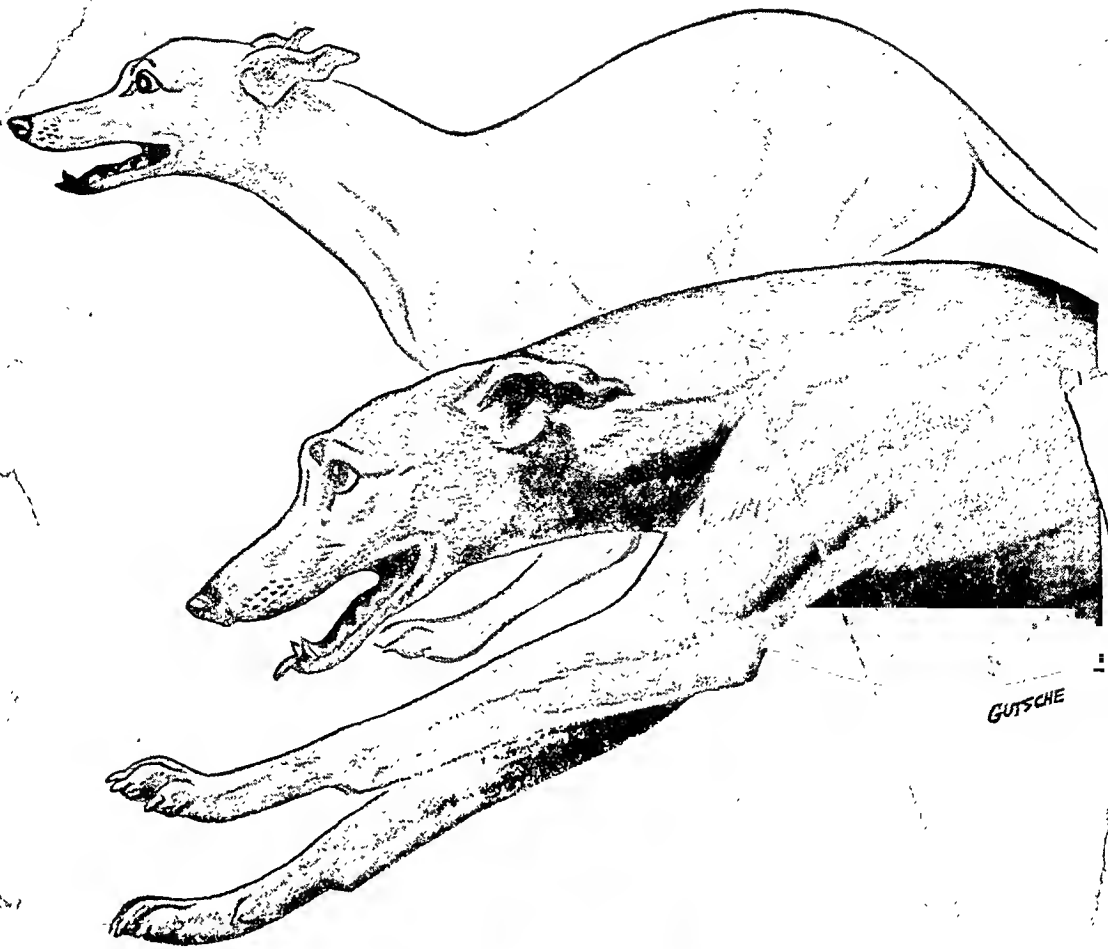
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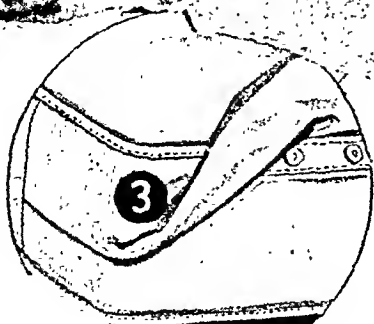
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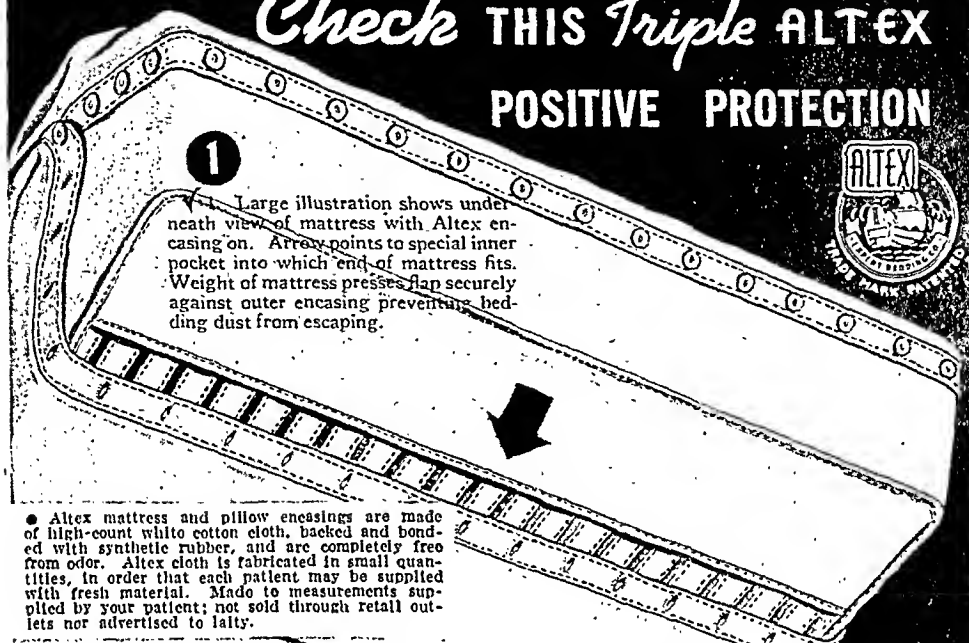
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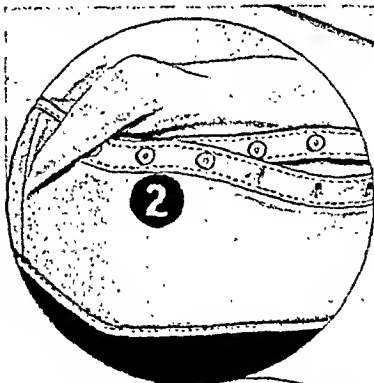


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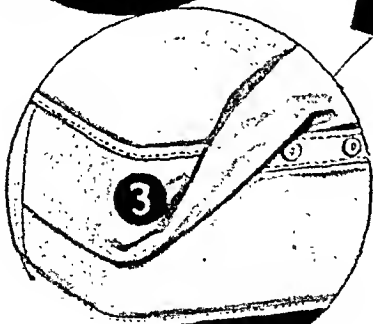
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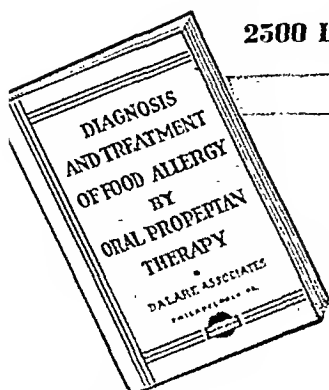
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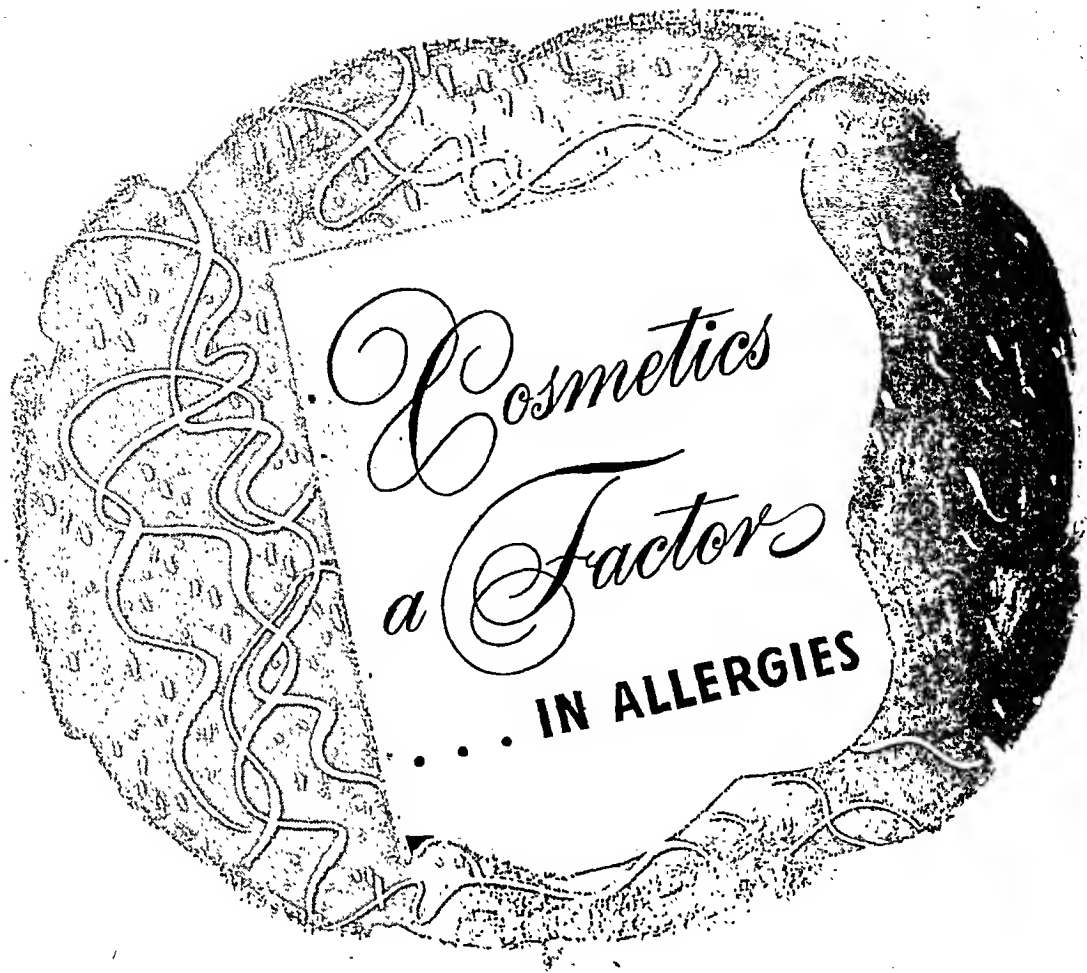
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## *Contents for March-April, 1946*

### CONTACT DERMATITIS.

- J. A. Rudolph, M.D., F.A.C.A., Miami, Florida*..... 79

### AMERICAN COLLEGE OF ALLERGISTS

- Preliminary Program, Annual Meeting..... 115

### ANTIGENICITY OF PROTEINS IN RELATION TO ALLERGY.

- William H. Welker, Ph.D., Sc.D., Chicago, Illinois*..... 123

### D.H.E.45 (DIHYDROERGOTAMINE) IN THE TREATMENT OF ALLERGIC MIGRAINE.

- Lt. Comdr. Norman W. Clein, MC, USNR, Seattle, Washington*..... 128

### FLEABITE REACTIONS.

- Milton M. Hartman, M.D., F.A.C.A., San Francisco, California*..... 131

### DEPARTMENT OF CLINICAL PATHOLOGY AND LABORATORY PROCEDURES:

#### Determination of Penicillin-Susceptible Strains of Bacteria.

- L. O. Dutton, M.D., F.A.C.A., El Paso, Texas*..... 137

#### Nasal and Sputum Smears.

- L. O. Dutton, M.D., F.A.C.A., El Paso, Texas*..... 138

- PHOTOGRAPH—Harry L. Rogers, M.D., President, 1945..... 142

### EDITORIAL:

- Blazing the Trail..... 143

- Our Guest Speaker..... 145

- College Ex-Service Members—An Appreciation..... 146

### PROGRESS IN ALLERGY:

#### Hay Fever.

- George E. Rockwell, M.D., F.A.C.A., Milford, Ohio*..... 148

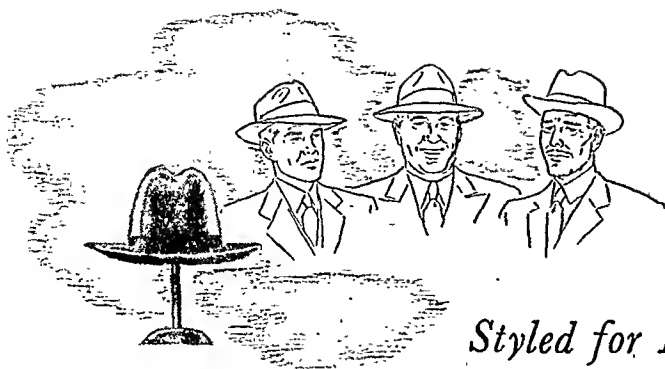
- QUESTIONS AND ANSWERS..... 157

- IN MEMORIAM..... 158

- NEWS ITEMS..... 159

- BOOK REVIEWS..... 161

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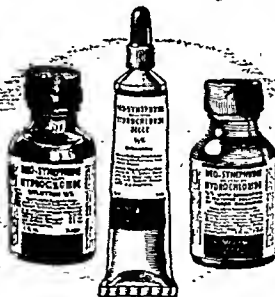
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March-April, 1946

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## CONTACT DERMATITIS

**As a Problem in the Army from the Standpoint of Diagnosis and Treatment, with the Presentation of Photographs and a Discussion of Several Interesting Case Records**

J. A. RUDOLPH, M.D., F.A.C.A.†  
Miami, Florida

"SKIN diseases are of greater importance in the military service than in civil life." This statement was made by Major General James C. Magee when he was Surgeon General. Although there are few deaths from skin diseases, they do result in a considerable loss of effective manpower and a partial incapacity of a number of personnel of many commands.

The latest available figures (1940) of the U. S. Army<sup>2</sup> indicate that skin diseases, exclusive of syphilology, produced 9.80 per cent of all admissions to the sick list and 10.41 per cent of all days lost. The figures for the United States Navy are very nearly the same. It is to be noted also that these figures are all peacetime statistics and that the diseases in these groups have always experienced a rapid relative increase during periods of military mobilization and actual combat. It is well known that the increase of skin disease is relatively greater than the increase of disease in other organs or systems. The major number of soldiers who report on sick call with skin disease remain ambulatory. The figures mentioned above, therefore, would indicate fewer than half their actual occurrence.

The skin is continuously exposed to a great number of ordinarily harmless substances, few of which are primary irritants, but which may induce contact dermatitis.<sup>27,33</sup> It is to be understood that the reaction of primary irritants on the skin is one of trauma and may be produced by

---

This article was presented before the Oliver General Hospital Chapter of the Military Surgeons, Augusta, Georgia.

†Recently relieved from Active Duty with the Army; formerly Chief Medical Service, Oliver General Hospital, Augusta, Georgia.

acids or alkalis. The resulting injury is not to be confused with the fact that anyone can be sensitized to contact with a dye or chemical, vegetable or weed, if the exposure is sufficiently prolonged and sufficiently intense. This resulting sensitization of the skin is often accelerated by a previous exposure to a primary irritant, as, for example, in the cook who washes his hands frequently with GI soap and becomes sensitive to the vegetables which he prepares.

The occurrence of contact dermatitis is probably greater than the incidence of all other allergic skin diseases, and as a group they constitute the most commonly encountered of all skin diseases.<sup>1,3,19,35</sup> Among the civilian population, the problem of contact dermatitis<sup>9</sup> had reached such proportion, particularly at the time when every man was needed, as to be considered a form of industrial sabotage. Louis Schwartz<sup>26</sup> of the United States Public Health Service has stated that more time is lost from work on account of occupational dermatitis than because of any other occupational disease. The increase in the number of these cases is due mainly to the increased industrial expansion which has taken place, the drive to attain peak production, and the secondary consideration given frequently to the matter of health hazards. The importance which this rising cost in manpower has reached has shown the need for immediate specific action. The Council of Industrial Health of the American Medical Association, realizing the great importance of this situation as it would affect our war effort were it allowed to continue, has sponsored an all-inclusive Industrial Health program.<sup>10</sup> The transfer into the armed forces of a considerable proportion of our working population, with the introduction of new environmental contacts, has made the problem of contact dermatitis in the Army one of great importance from the standpoint of diagnosis, treatment and final disposition.

The result of treatment in any disease depends upon correct diagnosis; this is especially true in contact dermatitis. The clinical and environmental history, symptoms, distribution of skin lesions, special tests and differential diagnosis will clearly point to the condition in question and enable one to treat properly a given problem and to evaluate correctly its cause and implications.

A few years ago, conditions of contact dermatitis were designated dermatitis venenata or occupational dermatoses, depending upon the nature of the excitants or the circumstances under which contact occurred. If, for example, the excitant was a constituent of a plant of the *Rhus*, such as the so-called poison ivy, poison oak or poison sumac, the condition was spoken of as dermatitis venenata, and the exciting substances in these plants were considered to be poisons. If, on the other hand, the dermatitis occurred among factory workers who handled certain chemicals such as T.N.T., iodoform or the dye paraphenylenediamine, the term occupational dermatoses was often used. Cran-

## CONTACT DERMATITIS—RUDOLPH

ston Lowe<sup>17</sup> in his book on Anaphylaxis and Sensitization, recognizing the identity of these conditions with those produced by the non-protein excitants of plants, describes them as "dermatitis venenata due to chemicals other than those contained in plants." However, when it was found that animals and also almost all city-born children under five years of age are completely insusceptible to the first contact with the strongest extracts of poison ivy, it became evident that the dermatitis caused by this plant was not due to any primarily toxic principle in it.<sup>32</sup> This observation left no further doubt that dermatitis venenata is a special instance of a specific cutaneous sensitivity which is acquired by and is exhibited upon surface contact with the excitants found in poison ivy.

The allergic nature of dermatitis venenata was demonstrated by the experiments of Brown, Milford and Coca,<sup>6</sup> Cranston Lowe<sup>17</sup> and especially Bloch<sup>4</sup> with primrose. These investigators could show that, whereas most persons are insusceptible to the juice or extract of primrose and other plants, many persons acquire a sensitivity to the plant after one or more exposures by surface contact. Bloch, using a concentrated extract of primrose, could sensitize all of the twelve subjects of his experiments.

### CHARACTERISTICS OF CONTACT DERMATITIS

Contact dermatitis differs characteristically from the inherited group of allergic diseases (bronchial asthma, hay fever, infantile or atopic eczema, urticaria, migraine)<sup>12</sup> and its ultimate diagnosis and proper treatment by the medical officer often depend wholly upon his recognition of these differences. A very significant difference between contact dermatitis and atopic eczema is the fact that an atopic hereditary influence seems to control the development of atopic eczema, but plays no part in the etiology of contact dermatitis. Individuals who develop atopic eczema usually have an atopic influence in their antecedent family history and often have hay fever or asthma at the time or later in life. However, contact dermatitis occurs where there is no atopic basis and may appear among the majority of those who are exposed for a long period of time to a particular excitant. Furthermore, in atopic eczema, usually no reaction occurs when the excitant is applied to the skin, but in contact dermatitis, the application of the exciting substance to any area of the skin usually causes a lesion of the same type. If the excitant is injected intradermally in an area which is free of lesions, wheal formations will usually occur in atopic eczema and skin-reacting antibodies are most often found in the blood. In the case of contact dermatitis, this wheal formation does not take place, and the skin-reacting antibodies are not present.<sup>7</sup>

There is no difficulty in tracing the simple instance of a contact dermatitis from which a soldier always suffers following the use of a certain shoe dye or which appears after a specific, dyed, fur-lined jacket is worn.

In such a case, if the patient has not already noticed the casual connection and acted accordingly, the medical officer simply advises the banishment of the offending material. On the other hand, when the patient is a pharmacist whose torturing eruption disappears if he avoids his daily contact with drugs, or when the attacks are seasonal and coincide with the pollination period of a hay-fever-causing plant, the problem is more complex. In either of these situations, if the medical officer is aware of the allergic nature of the dermatitis, not only must he resort to cutaneous tests in order to identify the exciting cause (plant or pollen) but he must choose the proper kind of test material and also the proper method of applying the cutaneous test.

An understanding of the symptoms and distribution of contact dermatitis will enable one to further clinch the diagnosis. Given a case of contact dermatitis, the history elicited will be one of sudden onset and the skin most severely involved will be that part of the body most exposed to the contactant. At first there will be an area of erythema limited to the area of contact, which is soon followed by edema, vesicle formation and subsequently weeping and crust formation. In cases which are not acute, the initial lesions need not be vesicles, but may be papular in character, with moderate edema and erythema. In several days this condition will result in a mild erythema and desquamation. If the process is one of a chronic nature, the area involved will present a bluish-gray discoloration. Later, thickening, lichenification, and desquamation will take place.

Marked itching is generally present in all stages of contact dermatitis, although during the height of the eruption, the pruritis may diminish noticeably. Secondary infection often complicates the picture, producing pustules, scabs and associated stinging, burning and pain.

Although no area of the skin is immune to contact dermatitis, certain areas of the skin surface are more easily affected. The exposed skin of the face, neck, especially the "V" area, the anterior part of the chest, upper extremities, legs and ankles are usually the sites of predilection. Specific contact allergens may be suspected when a dermatitis of the type described appears in a particular area of the body. It is, therefore, very important to establish the site of the first appearance of the dermatitis and its subsequent spread. The important areas<sup>34</sup> of involvement with possible contact allergens are shown in the accompanying table.

#### TESTS

The well-known skin tests<sup>25</sup> for determining the excitants of asthma, hay fever, infantile eczema, gastro-intestinal allergy and allergic headache are carried out by the intracutaneous injection of aqueous extracts of various materials or by rubbing the extracts into an abrasion in the skin produced with a needle or scalpel (scratch method). The exciting substances in these aqueous extracts are usually of protein nature and

## CONTACT DERMATITIS—RUDOLPH

### CHARACTERISTIC SITES OF ECZEMATOUS CONTACT DERMATITIS AND THEIR COMMON CAUSES\*

<i>Localization</i>	<i>Suggested Causes</i>
1. Scalp† and forehead	1. Scalp lotions; scalp tonics, pomades, etc., caps and hats and their bands, linings and other materials.
2. Eyelids (one of the most sensitive areas)	2. Numerous substances used on scalp, face, and hands, soaps, shaving lotions, creams, powders. Airborne volatile agents and dusts (plant pollens, insect sprays, gaseous substances; nasal sprays, cleaning fluids, antimoist preparations, perfumes, benzene; dusts from clothing, furniture; materials of dyed clothing, fabrics, furs, gloves, etc.).
3. Face in general	3. All possible materials transferred by hands or air-borne. All substances used on face, scalp, or hands. Shaving soaps, after-shaving lotions, etc., gas masks, etc.
4. Ears and retro-auricular areas	4. Scalp lotions, salves, spectacles, goggles, ear muffs, etc.
5. Nose and nasolabial areas	5. Nose drops, nasal ointments, sprays, etc., handkerchiefs, paper tissues, etc.
6. Lips and perioral areas	6. Mouthwashes, tooth pastes, powders. Sometimes certain foods (oranges, other citrus fruits and their juices).
7. Neck: front, sides and/or back	7. Collars, scarves, neckties, clothing, fabrics (wool and dyes) substances used on scalp.
8. Sides of neck, upper chest, wrists, cubital spaces, inner and anterior aspects of thighs, ankles, and lower legs and dorsa of feet	8. Typical of clothing materials and their dyes; "uniform" or "wool" dermatitis.
9. Hands, forearms, and face	9. Substances too numerous to list. Most occupational and industrial excitants. Substances encountered in military activities, plants (ivy, etc.); gasoline, greases, paints, chemicals, soaps, cleansers, gloves, steering wheels, instruments or substances encountered in hobbies or games; or topical medicaments applied to self or to others; all objects which may be touched, handled, held, or worn.
10. Trunk, various sites	10. Clothing, plants, underwear, night clothes, sweaters, bathing materials, soaps.
11. Perianal	11. Feces and decomposition products (cleanliness! thorough washing after defecation, no toilet paper), substances in enemas, suppositories, intestinal parasites, ingested foods (fruits, oils), topical medicaments, underdrawers, toilet paper, etc.

(See following page)

\*Based mainly on a table in Sulzberger, M. B., and Wolf, J.: *Dermatologic Therapy in General Practice*, Chicago; The Year Book Publishers, 1940.

†The scalp is often remarkably resistant to external irritants and allergens. Thus, dermatitis caused by substances used on the scalp often appears not primarily on scalp but predominantly or exclusively on other, more sensitive skin areas, such as eyelids, ears and retro-auricular areas, nape and other parts of neck, face in general, and even the hands.

# CONTACT DERMATITIS—RUDOLPH

## CHARACTERISTIC SITES OF ECZEMATOUS CONTACT DERMATITIS AND THEIR COMMON CAUSES

(Continued)

<i>Localization</i>	<i>Suggested Causes</i>
12. Penis and scrotum	12. Substances carried by the hands: plants, clothing, medicaments used for pediculosis, chemical prophylaxis, fungous infections, etc.; fabrics, finishes and dyes in underdrawers, pajamas, rubber and elastic supporters.
13. Thighs, legs, and ankles	13. Dyed materials and materials of trousers, underdrawers, socks, etc.; match boxes, cigarette lighters, coins, and other metallic objects carried in trousers, pockets, etc.; volatile and air-borne substances, dust (inside trousers), etc.; plants.
14. Lower portions of legs and feet	14. Shoes, socks, stockings (leather dyes, tanning agents, dyes, and finishes of materials, etc.); plants.
15. Feet (particularly dorsa of great toes), sides and dorsa of feet and sometimes soles (often with little or no interdigital involvement)	15. Shoes, leather dyes, tanning agents, shoe polishes, sock dyes and finishes, rubbers, etc.
16. More or less generalized eruptions	16. Any of the aforementioned agents may produce not only localized but generalized eczematous dermatitis. Also, medicaments taken by mouth or injected (arsenicals, quinine, salicylates, hexamethylenetetramine, etc.)
17. Contacts in the Army and location of the dermatitis	17.
(a) Face	(a) Gas masks.
(b) Chest and wrists	(b) Identification (dog) tags and metal buttons from uniforms and fatigue clothes.
(c) Arms	(c) Chevrons.
(d) Legs	(d) Paratrooper boots, GI shoes and socks.
(e) Generalized	(e) O.D. clothes (clothing dermatitis), oriental dye dermatitis <sup>18</sup> , penicillin contact dermatitis.

they are all antigens (capable of stimulating antibody production in animals).

In contact dermatitis due to vegetable or other excitants, on the other hand, the intracutaneous and scratch methods usually give negative results, especially with aqueous extracts, even when these extracts are prepared from the known excitant of the dermatitis. For this condition, it is necessary to use the surface contact or patch test which was first employed by the European dermatologist, J. Jadassohn.<sup>13,14,15</sup> This simple test merely reproduces the conditions of natural contact, and the resulting positive reaction represents nothing but the typical lesion of contact dermatitis.

The patch test may be carried out with the crude suspected material

## CONTACT DERMATITIS—RUDOLPH

(powder, leaf, fur, foodstuffs, chemicals) by placing it upon the skin (usually of the arm) and maintaining contact with wax paper or cellophane on a strip of adhesive plaster, or, as suggested by M. Walzer<sup>37</sup>, with a circle of cellophane rimmed with collodion or with the celluloid device of Aaron Brown.<sup>5</sup>

Aqueous extracts of vegetable excitants of contact dermatitis usually contain so little of the excitant that they do not cause reactions in the patch test. The reason is that these vegetable excitants are of fatty nature, and, therefore, only slightly soluble in water. However, they are easily extractable with fat solvent by evaporation, the fatty or oily residue is readily soluble in oils such as olive or almond oil. This oily fraction may be utilized for the purpose of eliciting patch test reactions.

The contact test is one of our most valuable clinical procedures, because it is a direct test of the clinically susceptible tissue, the epidermis; the positive reaction really reproduces the clinical lesions. The test seldom fails, if active and sufficiently concentrated material is used. Various techniques are available, depending upon the material being tested; the ideal procedure is the following:

- (1) An undiluted oily or resinous extract should be applied to a small area of untraumatized skin (rubbing is usually unnecessary); the area is covered, for protection and for limitation of reaction, as noted above, with a square of white blotting paper about one-quarter inch in diameter set in the center of a large square of cellophane or wax paper and then a still larger square of adhesive plaster.

- (2) A similar technique can be employed if the test material consists of dry powder. The dry powder is applied directly to the skin.

- (3) Raw materials may also be used, such as a leaf which has been crushed before being placed on the skin, a piece of fur, suspected pollen, or dust. Such tests are, of course, less expensive and more readily available than those with the extracted oils and they are probably just as reliable. However, after a positive response with the raw materials, if specific treatment is contemplated, it is advisable to do the patch test again, using the extracted oil or an alcoholic extract.

Contact is maintained for twenty-four to forty-eight hours. The site should be kept under daily observation for five days before the reaction can be safely considered negative. When the reaction begins early, the patient should be instructed to take off the patch or report to the medical officer as soon as distinct itching is noticed. The oil should be removed thoroughly with alcohol or ether. This precaution is advised to prevent any unnecessary dermatitis.

Like other forms of allergy, contact dermatitis may be due to more than one excitant, and the patient may be found sensitive by contact test to an excitant which is not producing the clinical dermatitis under

## CONTACT DERMATITIS—RUDOLPH

investigation at the time. For example, a painter may suffer severe dermatitis and a contact test may show that he is highly sensitive to poison ivy; yet, his dermatitis may not be due to poison ivy, but to the turpentine in his paints. In other words, it is important, before treatment is begun, that the result of the patch test be corroborated by the clinical history.

A positive reaction indicates hypersensitivity of the skin to the particular substance tested, but does not necessarily indicate that this substance is the cause of the existing dermatitis. The test must reproduce some phase of the existing dermatitis, such as erythema, edema, vesiculation and intense itching. It must further be indicated in a history of exposure to this substance.

In a negative reaction one must be certain that the substance tested is the one suspected according to the history, and that it is in the proper concentration. Also the area tested may have undergone spontaneous desensitization. It may be necessary to test a former area of dermatitis, since it may have become hypersensitive. The "V" of the neck is often productive of positive patch tests<sup>30</sup> when the arms are negative. This is especially true of facial contactants.

Polyvalent hypersensitivity in contact dermatitis is as common as it is in atopic eczema and makes for certain difficulties in deciding which substance is responsible; here the history will give the needed clue. Also, trial and error tests will assist in making the final decision.

### DIFFERENTIAL DIAGNOSIS

The differential diagnosis is important, as there are a number of dermatoses which may be confused with contact dermatitis, as, for example, soldiers with a fungous infection<sup>20</sup> of the feet, together with a trichophytid<sup>38</sup> of the hands, a commonly made diagnosis, which is probably incorrect in at least half of the cases. A contact dermatitis of the feet, i.e., shoe dye dermatitis, may also produce vesiculation of the palms. Another vesicular eruption of the palms is cheiropompholyx, found chiefly in women, especially in those of a psychoneurotic background, particularly during the summer months. With atopic eczema, there is a personal or family history of clinical allergy. Nummular eczema, sharply margined, coin-shaped plaques studded with punctuate vesicles, is found usually on the dorsal surfaces of the hands. Seborrheic eczema is associated with involvement of the palms and soles. Here the history and involvement of other areas are significant. There are also the skin diseases such as herpes simplex or herpes zoster which must be considered. The secondary skin lesions known as bacterids<sup>23,31</sup> which are the result of a toxic reaction from some focus of infection may resemble contact dermatitis, especially if the hands or feet are involved. An eczematoid dermatitis from primary irritants such as rubefacients, turpentine,

## CONTACT DERMATITIS—RUDOLPH

gasoline, benzene, acids, alkalies, may be differentiated by a careful history, as noted above. Infectious eczematoid dermatitis such as impetigo, ecthyma, and simple folliculitis must also be kept in mind. Yeast infections, associated with onychia, paronychia, perleche and intertrigo, presenting an erythematous, glazed skin with scaling, must not be overlooked. A long standing scabies, dermatitis herpetiformis, erythema multiforme, drug eruptions, lichen planus, psoriasis, syphilis, and others may be confused with a contact dermatitis if the examination is not of the most painstaking character.

### TREATMENT

It should be born in mind that the treatment of contact dermatitis consists primarily of avoidance of the excitants to which the individual is allergic by contact and substitution or replacement if necessary and if possible of other substances to which he is not sensitive. However, it should also be remembered that having developed this highly sensitive skin, he may later become sensitized to the new materials. Where sensitization is to plants and avoidance is impossible, prophylactic measures and desensitization with oil extracts may be used.

Most plant extracts are available not only for the patch test but also for treatment, and it has been gratifying to discover that the results of specific treatment of contact dermatitis due to plants are as good as those obtained in the treatment of hay fever due to pollens. In this service command, the following method of treating poison ivy was employed and has been developed by Col. S. W. French, Surgeon to the Fourth Service Command, and Major Lawrence J. Halpin.<sup>11</sup> It is certainly the most convenient in the Army.

"A five per cent alcoholic extract of poison ivy leaves is prepared for active treatment. This is considered as a master extract and will deteriorate rapidly if diluted. In an undiluted form, its potency, as evidenced by a bright green color, will remain indefinitely. Institution of active treatment should be made and continued in the following manner:

"(a) Use a dry tuberculin 1 c.c. syringe and needle in order to prevent the addition of any water to this master extract.

"(b) Withdraw 0.1 c.c. of this master extract. Dilute it to ten times by the addition of 0.9 c.c. of normal saline or similar diluting fluid. Pull out the plunger a short distance to allow thorough mixing of the extract and the diluent.

"(c) In order to insure accurate dosage, all but the amount to be given in that one treatment is to be forced from the syringe prior to administration. The site of injection should be the lower third of the arm.

"(d) Improvement will usually be seen after the first or second treatment, and the dosage is increased gradually with each treatment, depending upon the amount of general reaction and the appearance of symptoms. The injections are given daily or every other day, according to the degree of reaction and the appearance of lesions.

"(e) The following is a brief schedule which may be used as an indication of the amount to be given at each treatment, using the above method of dilution:

First day: 0.1 c.c.  
Second day: 0.2 c.c.,  
Third day: 0.25 c.c.

Fourth day: 0.3 c.c.  
Fifth day: 0.35 c.c. (if necessary)  
Sixth day: 0.4 c.c. (if necessary)

## CONTACT DERMATITIS—RUDOLPH

Great care must be taken in the administration of this extract to prevent an increase in the severity of lesions after an original improvement has been noticed. If there has been an exacerbation of the symptoms, it is best not to increase the dosage, but to decrease it or to repeat the same dosage. Mix each individual dose immediately before administration.

"(f) The above schedule need not be followed in each individual case, since it may be found that some individuals will respond to only two or three injections, whereas others may require four to five. Satisfactory results will usually be obtained by the proper use of this extract."

Other varieties of plant dermatitis may be treated successfully in the above manner. A single injection of 0.5 c.c. of 1 per cent solution of the oil of snap dragon in sterile almond oil has within twelve hours caused a complete disappearance of itching in a florist sensitive to this plant. In another instance, in civilian practice, (sensitivity in a florist to *Gaillardia*)<sup>22</sup> after three weekly injections of the oil solution had resulted in the disappearance of the dermatitis (although the patient continued to handle the plants), the treatment was discontinued in order to determine the longest interval of time at which the injections could be spaced without risk of a recurrence of the symptoms. After two months the skin lesions began to develop, indicating that about six weeks could be taken as the proper interval in that case.

Spain and Cooke<sup>28,29,30</sup> state that best prophylactic protection is obtained by beginning the injections early in April and continuing until frost. If alcoholic extracts are used, the first five doses (0.1 c.c. of 1-100, 1-50, 1-20, 1-10 and 1-5 dilutions of a 10 per cent alcoholic extract of the dry leaf) should be injected at weekly intervals. Thereafter, the fifth dose is repeated, at first at two or three weeks, then at monthly intervals.

If the ivy extract is administered in an oily base such as almond oil, the first dose can be about five times the maximal dose of the alcoholic extract and this dose can be repeated advantageously at two- or four-week intervals throughout the season. Evidently, the oily nature of the menstruum serves to reduce the rate of absorption of the injected extract and thus extends its effect over a longer period of time.

Spain and Cooke<sup>28,29,30</sup> also report that by quantitative patch test, no diminution in the skin sensitivity of a susceptible person could be detected after the successful application of specific prophylactic treatment by the injection method. Hence, as is also the case in hay fever, the degree of clinical tolerance to the excitant of contact dermatitis cannot be judged by the result of the quantitative skin test. However, they state that only four of the 98 patients so treated failed entirely to obtain relief from attacks of ivy dermatitis.

It is of some practical interest to medical officers in the United States to know the specific relationship of the three well-known excitants of plant dermatitis in this country, i.e., poison ivy, poison sumac, and poison oak. The close botanical relationship of these three plants would suggest a corresponding similarity of the active substances in them and this has

## CONTACT DERMATITIS—RUDOLPH

been verified by Henry W. Straus in some convincing experiments. Straus<sup>32</sup> sensitized newborn infants to poison ivy by skin surface application and then tested these sensitive children with extracts of the other two plants. The results of these tests were positive in all cases. These observations indicate that specific treatment of sensitivity to these three plants can be carried out with the extract of any one of them.

The specific treatment of contact dermatitis<sup>2</sup> due to animal contactants follows, in general, the therapy of Rhus dermatitis by injection of the extracted oily excitant. The allergenic oils are slightly soluble in water; in fact, the injection of saline pollen extracts has in a few instances caused the disappearance of a dermatitis due to the corresponding oil. However, in many patients a larger dose of the excitant oil is required for complete protection than can be provided in an aqueous medium. Furthermore, it is important that the oil be dissolved in a menstruum in which its specific activity will be preserved for a long period of time. Such a menstruum is sterile almond oil, which also possesses the valuable property of retarding the absorption of the dissolved excitant, thus extending its action over a longer period.

The routine of treatment differs in seasonal and non-seasonal cases:

1. If the dermatitis is seasonal, begin the injections about three weeks before the expected onset of symptoms. Give three doses at two-week intervals; a fourth dose may be given in mid-season and this should usually be sufficient. If lesions begin to appear later, further injections should be given.

If the treatment of a seasonal dermatitis begins during the season, (i.e., the lesions have already appeared), the first three injections, given at one to three-day intervals, may cause a rapid disappearance of the itching. Flare-ups may also occur, and it may be necessary to reduce the dosage. After the immunizing effect of the injected oil has been established, the healing of the existing lesions may require a period of weeks. This is in accord with the experience regarding the spontaneous healing of ivy poisoning after a single contact; these lesions sometimes persist for months after such contact. It must be understood that symptomatic treatment should be given during this healing period to assist in overcoming the irritation and in hastening recovery.

2. If the patient is continually exposed to the excitant, as in the case of a painter sensitive to turpentine, or a florist sensitive to a hothouse plant, the first three doses should be given at the shorter intervals (one to three days) and the injections should then be continued at five- to seven-day intervals until the lesions have disappeared. The frequency of the injections depends on the case, and no universal schedule can be given, because the degree of sensitivity and degree of tolerance varies with each individual and knowledge of what schedule should be followed must be based on experience.

## CONTACT DERMATITIS—RUDOLPH

3. It is to be understood that injections for metallic or other inorganic substances still await proper dosage and technique. At the present time, avoidance of these contacts is the method of choice. This is in accord with the experience of leading allergists and dermatologists.



Fig. 1. Case 1. Dermatitis of chest and wrists from metal contact (identification tags—"dogs", metal buttons on fatigue clothes).

The accompanying photographs are a representative cross section of the various cases of contact dermatitis which have been seen in our outpatient clinic and in our hospital service within the past year. Some of the more unusual ones are subsequently discussed.

### DEMONSTRATIVE CASE RECORDS

*Case 1.*—The first case illustrated by photographs is that of a twenty-nine-year-old soldier who first developed a rash while he was out on maneuvers in 1941. The rash appeared first on his right wrist and it became generalized so that he had to be hospitalized at Camp Forest Station Hospital. His condition subsequently quieted down during his hospital stay, but he had to report from time to time to the outpatient clinic for repeated attacks of dermatitis on his chest and wrists, until he was again hospitalized on 27 June, 1943. Because his skin condition failed to respond to treatment, he was transferred to Oliver General Hospital 22 July, 1943 for further study, treatment and disposition.

Contact allergic history was significant in that the patient recalled always being sensitive to metals, especially during civilian life, when he was working as a mechanic in a garage. He also stated that he knew he was sensitive to coins of any type.

Physical examination, aside from his dermatitis, was found to be essentially negative. The skin of the chest, abdomen and wrists was studded with reddish-blue

## CONTACT DERMATITIS—RUDOLPH

papules varying in size. The eruption was in various stages, revealing macules, papules, dried vesicles, many scratch marks and pigmented areas on the skin.

Laboratory examinations, including a complete blood study, serological tests and urinalysis, were negative. The scrapings from areas of the lesions revealed no fungi.



Fig. 2. Case 2. Dermatitis in a paratrooper from leather boots.

During the patient's stay in the hospital, he began to improve under mild soothing therapy, consisting principally of an aqueous lotion of zinc oxide, talc, bentonite, glycerin and water. When the skin showed sufficient improvement, he was then patch tested and found markedly sensitive to his metal "dog tags" and to the metal buttons of his fatigue uniform. He was also found very sensitive to mercury, copper and arsenic by patch testing. Various experiments, including the covering of his identification tags with chamois skin, cellophane, and x-ray film, were attempted in order to prevent recurrences of his dermatitis, but with little success, as the eruption would recur within twenty-four hours to seven days. Since there is no recognized treatment for metals other than avoidance, the failure of this technique made it necessary to discharge this man from the service because of his marked allergy to the various metals. A similar case was recently reported in *The Military Surgeon* of January, 1943, by Lt. Paul N. Unger, MC, U. S. Army.

## CONTACT DERMATITIS—RUDOLPH

*Case 2.*—A nineteen-year-old white soldier was admitted to Oliver General Hospital in July, 1943 complaining of a severe rash involving his feet and the lower two-thirds of his legs. This patient was a paratrooper and states that about one month after he started making his training jumps he developed some blisters

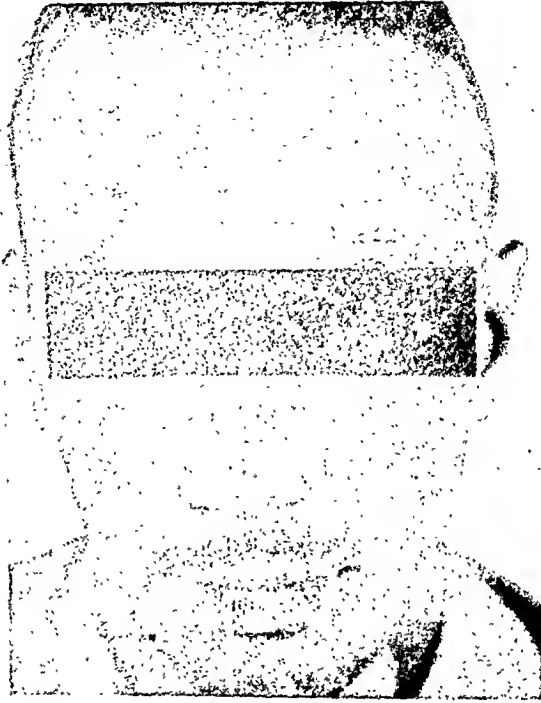


Fig. 3. Case. Dermatitis from contact with gas mask.

on his legs and feet. He reported on sick call for the blisters, which were very itchy. He states that his condition was diagnosed as athlete's foot and treatment was given for that condition. Because his dermatitis continued to become more severe, he was transferred to this general hospital for further treatment and disposition.

His contact and allergic history was essentially negative.

Physical examination, except for his dermatitis, was essentially negative. Over the skin of his feet there was a markedly pigmented, vesiculating, crusting dermatitis involving the dorsum of both feet and legs in the region of the ankles. There was no evidence of involvement on his soles or between his toes to suggest an epidermophytosis. In addition, there were macular, papular and vesicular lesions which covered the arms; crusts, probably due to secondary infection, covered most of the skin of the legs. The skin of the rest of the body was clear.

Laboratory examinations, including complete blood studies, serological tests and urinalysis were essentially negative. Smears from the skin lesions revealed no fungi.

It was our impression from the patient's history and physical findings that we were dealing with a contact dermatitis primarily due to the leather of his paratroop boots, which reached over halfway up his legs. This opinion was confirmed by patch tests. In these patch tests a piece of the tongue of his boots, as well as small pieces of material from his socks and other articles of clothing,



Fig. 4. Case 4. Dermatitis caused by repeated application of adhesive tape to feet and ankles with resulting, almost fatal, constitutional reaction.

was applied to the skin of his back. When these patches were removed for inspection, there was a marked reaction at the site of the leather contact. Under mild local medication, consisting of an aqueous solution of zinc oxide, talc, starch, bentonite and glycerin, his dermatitis rapidly improved, and since this patient was very eager to remain with his unit, a shoemaker was found who lined his boots with an impervious material, so that he was able to return to full duty. A recent letter from this soldier found him overseas and up to the present time he has had no recurrence of his dermatitis.

*Case 3.*—This photograph illustrates a type of dermatitis which is not infrequent in the Army. The patient in this photograph presented himself to the outpatient clinic of Oliver General Hospital with skin lesions on his forehead, on the lateral aspects of his face and on his chin. This dermatitis was thought to be due to contact with the rubber from the gas mask which he wore. This sensitivity to rubber was proven by a positive result to a patch test. A small segment of rubber from a gas mask was placed in contact with the patient's skin. After a period of forty-eight hours it was removed, revealing a marked reaction to the rubber. Other contactants, to which he was tested at the same time, gave negative results. An

## CONTACT DERMATITIS—RUDOLPH

effort was made in instances of this type to obtain a non-irritating rubber gas mask. A request regarding such a mask was made to the commanding officer of the Edgewood Arsenal and a reply was received from Brigadier General W. C. Kabrich, C.W.S., indicating that no such gas masks were available. Toxicity tests



Fig. 5. Case 5. Dermatitis caused by lubricating oil and grease, carried from hands to ears.

are made at the Edgewood Arsenal to eliminate primary irritants, but there are a number of individuals who will become sensitive to the materials of the gas masks. It was recommended by this officer that especially sensitive individuals be transferred to duty that would not require the wearing of a gas mask.<sup>10</sup> This advice was followed in the disposition of the soldier in this case.

*Case 4.*—A twenty-three-year-old soldier was admitted to Oliver General Hospital 2 October, 1943. On admission he appeared acutely ill with generalized exfoliative type of dermatitis associated with intensive itching, stinging and burning. The

## CONTACT DERMATITIS—RUDOLPH

patient stated that approximately six weeks previously he first noted an itching irritation about his ankles. This dermatitis appeared to be the result of several applications of adhesive tape to his feet and ankles. The adhesive tape had been applied because he had reported on sick call complaining of painful feet and



Fig. 6. Case 6. Dermatitis from sulfathiazole ointment and subsequent susceptibility to many greasy ointments, always with a return of symptoms.

ankles, especially after prolonged hiking. Although the pain in his feet and ankles had improved, and in spite of the irritation of his skin, the application and re-application of adhesive tape to his feet was continued for about two weeks. The

## CONTACT DERMATITIS—RUDOLPH

eruption spread from the legs to the rest of the body, including the face, trunk and extremities, and he became very toxic.

His contact and allergic history was essentially negative.

Physical examination revealed an acutely ill white soldier who appeared toxic



Fig. 7. Case 7. Dermatitis due to pollen skin sensitivity to timothy and ragweed in a soldier who failed to respond previously to poison ivy extract.

with a generalized "oozing," vesiculating, desquamating dermatitis with marked itching. It was also associated with marked purpuric areas most noticeable over the lower extremities and lumbar region of his back. His lips were dry and crusted, but there were no apparent lesions in the mucous membrane of his mouth.

Laboratory examinations, including complete blood studies, revealed RBC 3,770,000, WBC 17,200, Hemoglobin 70, serological tests negative, normal blood

## CONTACT DERMATITIS—RUDOLPH

chemistry studies, and several granular casts and much mucus, but no blood, in the urine.

Because of the severity of this patient's dermatitis with marked toxic manifestations, he was placed on the critically ill list. He was given intravenous saline and



Fig. 8. Case 8. Dermatitis from dye in socks with superimposed secondary infection.

glucose and 200 mg. of cevitamic acid daily. Fluids of all types were encouraged, and a high caloric, soft diet was ordered. Medication by mouth was withheld, because of the possibility that drugs, especially of the sedative type, might accentuate this dermatitis. Local applications of boric acid and alum in the proportions of five parts of boric acid to three parts of alum in five hundred parts of water was used over his entire body, but this was apparently somewhat irritating. An aqueous lotion consisting of zinc oxide, talc, bentonite, tincture of ferric chloride and water was applied to his skin by means of a soft paint brush which had been previously sterilized. Within a period of seven days, the patient responded to the above outlined treatment, and he was removed from the critically ill list. His improvement continued satisfactorily and by Christmas of 1943 he was able to go home on sick leave. Upon his return, a mild dermatitis of his legs and ankles persisted in spite of all the various treatments which were used.

At this time his screen test to adhesive tape revealed an extremely marked hypersensitivity to the tape. It was, therefore, concluded that on the basis of his past personal history and his marked sensitivity to adhesive tape, that this was a case of a severe contact dermatitis due to adhesive tape. In January of 1944 he



Fig. 9. Case 9. Dermatitis due to Whitefield's ointment in a soldier with trichophytosis whose symptoms were accentuated with its application and who proved to be sensitive to salicylic acid.

was transferred to a Veterans Facility in order that his treatment might be completed.

*Case 6.*—This patient is a thirty-one-year-old soldier who was admitted to Oliver General Hospital in August, 1943, with a diagnosis of cellulitis. His history stated that this dermatitis followed an injury to his left leg, which occurred while he was out on maneuvers. He was admitted on the surgical service, and after examination was promptly transferred to the Allergy Department for study and treatment. It was found on studying the records that the injury was treated with sulfathiazole ointment and after this treatment he developed an itching eruption which spread rapidly, involving the lower half of his left leg. Treatment with various types of ointments failed to stop the spread of this dermatitis.

## CONTACT DERMATITIS—RUDOLPH

There were no associated constitutional symptoms.

His contact and allergic history was negative and there were no significant findings in his past history.

His physical examination was essentially negative except for the dermatitis.



Fig. 10. Case 10. Dermatitis due to contact with wool and marked sensitivity to lanolin.



Fig. 11. Case 11. Dermatitis due to leather or dichromate from army shoes, beginning on feet and becoming generalized.

## CONTACT DERMATITIS—RUDOLPH

Over the skin of the lower half of his left leg there was a widespread eruption which appeared very acutely inflamed. Superimposed upon an erythematous base, there were numerous small pustules and vesicles which were very painful and itchy. Most of these lesions were covered by crusts, presumably the result of



Fig. 12. Case 12. Dermatitis in central technician from handling a dental compound—"Coe-loid." Both hands are involved, the left hand being most affected.

secondary infection. Laboratory examinations, including complete blood studies, serological tests and urinalysis, were essentially negative. Smears from the skin lesions showed no fungi.

It was our impression that the patient had a contact dermatitis masked by the therapy which he had received and by the presence of the secondary infection. A solution consisting of five parts of boric acid and three parts of alum in five hundred parts of water was applied locally in compresses. His condition was so improved within a week that it was felt that a ten per cent boric acid ointment might complete the treatment. However, instead an exacerbation of the dermatitis occurred. Another exacerbation occurred when anhydrous lanolin was used. Recovery was finally effected by the use of a soothing lotion consisting of zinc oxide, talc, starch, bentonite, glycerin and water. During this patient's stay in the hospital, he was patch tested to sulfathiazole, petrolatum and lanolin. In each case positive reactions resulted. This soldier was returned to full duty and advised about the necessity of understanding the nature of his sensitivity. A recent communication from him states that he has remained in good health.

*Case 7.*—This twenty-six-year-old white soldier gave a history that since 1939 he had a recurring dermatitis during the summer. This dermatitis began with a few small pimples on his face and arms and finally resulted in a dermatitis all over his body, necessitating hospitalization. The condition would often persist well into the end of the summer season. Since his entrance into the service, the condition has continued to recur and because of it he has spent two sessions in different hospitals for prolonged periods of time. Each time he was given intensive treatment with poison ivy extracts.

## CONTACT DERMATITIS—RUDOLPH

His contact and allergic history prior to coming into the service had been positive, as evidenced by his statement that he had always had a very sensitive skin, especially when he went out into the country and was exposed to the various grasses and weeds.

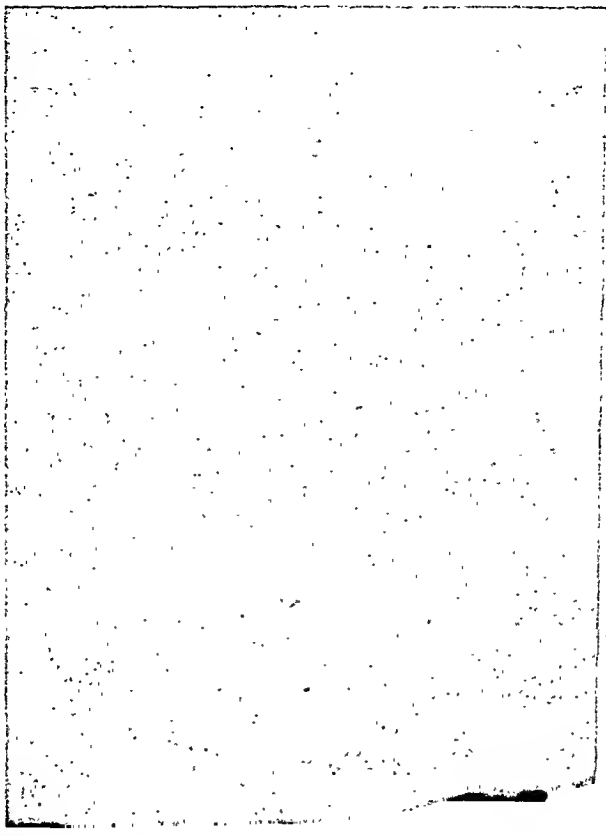


Fig. 13. Case 13. Dermatitis from money belt.

Physical examination, except for his dermatitis, was essentially negative. At the time of examination in May, he was beginning to have a dermatitis, most noticeable on his face, consisting of vesicles and papules which were very itchy. He stated that very soon this would become generalized, if it followed its previous course.

Laboratory examinations, including complete blood studies, serological tests and urinalysis were essentially negative.

It was our impression that we were dealing in this patient's case with a pollen dermatitis, rather than a poison ivy dermatitis, especially in view of the fact that poison ivy therapy failed to evoke a favorable response. Patch tests with the oily fractions of timothy and ragweed revealed moderately severe positive skin tests, as is shown on the photograph. Soothing therapy to the skin of his face prevented the condition from becoming more severe during the summer of 1943. An emulsion of timothy and ragweed pollen in sterile almond oil resulted in improvement and there were no additional generalized symptoms occurring during the remainder of the summer. At this time he is not under our care and we do not know of his

## CONTACT DERMATITIS—RUDOLPH

subsequent reactions. As reported in a previous article, this technique was successful in a severe case in private practice.<sup>24</sup>

*Case 8.*—A twenty-four-year-old white sergeant was transferred from the Fort



Fig. 14. Case 14. Dermatitis from toilet seat with secondary pyoderma.

Meyers Station Hospital in Florida where, he states, he first developed a skin eruption on his feet and legs. He was treated in the battalion dispensary in November of 1942 without improvement. He was then hospitalized for two months without improvement and was sent to Lövell General Hospital, from where he was discharged as cured and sent back to full duty. Because his dermatitis reappeared again after a few weeks on duty, he was returned to the Station Hospital in August, 1943, where he received sulfathiazole ointments, cod liver ointment and five x-ray treatments without improvement. He was then transferred to Oliver General Hospital 30 September, 1943, for further study, treatment and disposition.

Contact and allergic history was negative, as was the remainder of his past history. Physical examination revealed essentially negative findings, except for the dermatitis of his feet and legs. The skin of the dorsum, ankles and lower third of both legs revealed encrusted areas with marked scaling and "oozing." The basic lesions were papules, pustules, crusts and scabs with fissures implanted upon an erythematous base. The pustules and crusting lesions were presumably the result of secondary infection. There were no apparent lesions between his toes or on the soles of his feet, although he had some small lesions of a pustular character on his hands, especially on the lateral aspects of his fingers.

Laboratory examinations, including complete blood studies and serological tests, were essentially negative. Smears from the skin lesions showed no fungi, but staphylococci were found. He did not react to trichophytin or oidiomycin skin tests intradermally.

## CONTACT DERMATITIS—RUDOLPH

It was our impression that the patient had a contact dermatitis masked by the therapy which he had received and by the presence of secondary infection. Potassium permanganate in a 1-5000 dilution was used at the outset with poor results. The area involving his lower extremities was then treated with three-

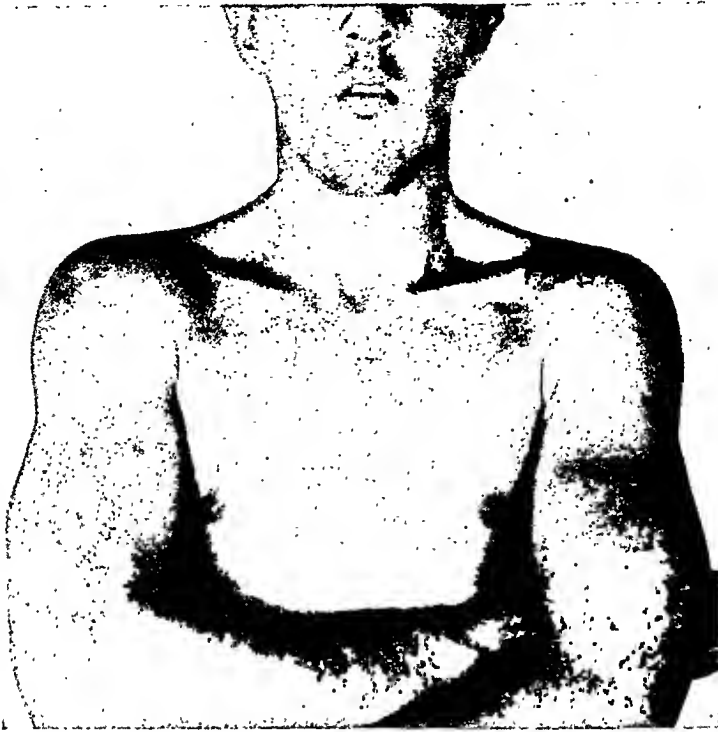


Fig. 15. Case 15. Dermatitis on outer aspects of the middle of the arms. Note vesicular character of lesions. Dye in chevrons proved to be contactant responsible.

per cent sulfathiazole in an aqueous lotion consisting of zinc oxide, starch, bentonite, and glycerin. Poor results were obtained. The condition continued to be troublesome, drying up partially at times, then again breaking down.

In view of the chronicity of this condition and the finding of positive patch test reactions to GI wool socks and O.D. material, and in the absence of a reaction to undyed wool, it was our opinion that this soldier was suffering from a dye dermatitis complicated by secondary infection. Inasmuch as he was not wearing his dyed socks or wool O.D.s at this time, the important problem here was to correct the persistent infection. Plaster casts were applied to both legs and feet for the purpose of avoiding further irritation of his skin by scratching and for the possibility of healing by bacteriophage action. These casts were kept on his extremities for one month, during which time a very pronounced odor developed, so that the casts were removed. The improvement of his legs was so advanced, that mild local applications of boric acid solution with alum, as described above, completely cleared up the condition. This patient was then returned to full duty, with instructions that he wear nothing but undyed socks. No report as to the ultimate outcome or recurrence is known at this time.

*Case 12.*—A twenty-six-year-old white corporal developed a dermatitis about April of 1943. It started as small blisters on the thenar eminences of both hands. The condition would dry, recur and finally spread to the fingers. This was as-

## CONTACT DERMATITIS—RUDOLPH



Fig. 16. Case 16. Dermatitis from camphor-phenol eutectia superimposed on an existing contact leather dermatitis, previously diagnosed and treated as trichophytosis.



Fig. 17. Case 17. Dermatitis from gasoline in crew member of B-25, who was plane mechanic.



Fig. 18. Case 18. Dermatitis from a soap highly advertised for B.O.



Fig. 19. Case 19. Dermatitis of legs from dye in trousers. There was no apparent sensitivity to the material.

## CONTACT DERMATITIS—RUDOLPH

sociated with mild itching at the outset, and later in the course of the condition the itching became marked. He had many types of local treatment, including light therapy, which helped his dermatitis to dry up, but he often found that following the use of soap and water the condition would flare up. The soldier stated that the



Fig. 20. Case 20. Dermatitis from cutting oil used in the operating of machine tools; secondary pyodermitis was present. Distribution was symmetrical, extensor surfaces of both forearms being involved. Factical element was strongly suspected.

dermatitis first seemed to appear after he began to use an impression compound known as "Coe-loid," while he was working in the dental clinic as an assistant. In the previous six weeks he had had no contact with this impression compound, and the irritability of his hands seemed to be quieting down.

Contact and allergic personal history was negative, but he stated that his mother had hay fever. His remaining past history was negative. Physical examination, except for the dermatitis, was negative. Over the skin of the hands, bilaterally involving principally the fingers of both hands, most markedly on his left hand, he presented a profuse eruption in several stages. Superimposed upon an erythema-

## CONTACT DERMATITIS—RUDOLPH

tous base there were pustules and vesicles with marked desquamation, cracking and fissuring of the skin of his fingers and considerable stiffening of his fingers from disuse.



Fig. 21. Case 21. Dermatitis involving popliteal space and a large part of thigh and leg of but one lower extremity in an asthmatic of recent occurrence and negative atopic history. Elastic knee support was contactant involved.

Laboratory examinations, including complete blood studies, serological studies and urinalysis, were essentially negative.

He gave a moderate reaction to Coe-loid dental compound as well as slight reactions by intradermal testing to asparagus, sweet potatoes, tomatoes and radishes. The various skin tests were accomplished because of a mild vasomotor rhinitis of which he complained and which examination verified. It was our opinion that the patient had an interesting skin condition probably due originally to intimate contact with this dental compound, with superimposed secondary infection. The superimposed secondary infection was cleared up first by the use of soothing medication consisting at first of a potassium permanganate solution of a 1-5000 strength for one week, followed by the use of a zinc oxide, starch, bentonite, glycerin and water solution, and subsequently, massage to his fingers. The best treatment for a contact dermatitis of this type is avoidance. Where avoidance is not possible, rubber gloves may be tried. In this case, the soldier was returned to duty with a recommendation for reassignment where he would not be required to handle the offending contactant.

## CONTACT DERMATITIS—RUDOLPH

*Case 15.*—A twenty-five-year-old white Staff Sergeant was admitted to Oliver General Hospital in August, 1943, with a dermatitis involving the outer aspects of both arms. He stated that during the previous hospitalization his condition had



Fig. 22. Case 22. Dermatitis from arch supports worn inside shoes, secondary to subacute epidermophytosis and marked hyperidrosis.

improved somewhat under the various types of medication which had been applied, but that the lesions recurred quite regularly. He could give no clues as to the cause other than the fact that he had to report on sick call frequently for a local type of medication because of the recurrence of the blisters and the severity of the discomfort.

Contact and allergic history was negative, except for a history of occasional dermatitis from poison ivy. This dermatitis was always mild; therefore, he never took any medication for it. The remainder of his past history was negative. Physical examination, except for his dermatitis, was found to be negative. Limited to the skin of both arms, involving the lateral aspects of the mid-portion of the arms, was a moderately severe dermatitis showing a macular, papular, vesicular eruption on a mild erythematous base, with some desquamation, scaling and crusting.

Laboratory examinations, including complete blood studies, serological tests and urinalysis, were essentially negative. A smear from the lesions was negative for fungi.

Patch tests to the clothing, including socks and khakies, were negative, as were the reactions to leather and various chemicals. However, it occurred to us, because of the unusual distribution of the lesions, that this might be a dye dermatitis produced from the dyed portion of the cloth to which his chevrons were sewn. A portion of this dyed material was used in patch testing and to this he gave a moderate to marked reaction. On the basis of this positive finding, it was our opinion that we were dealing with a contact dermatitis. After local treatment with boric acid and alum compresses for approximately one week,

## CONTACT DERMATITIS—RUDOLPH

followed by soothing, protecting lotions containing zinc oxide, starch, bentonite, talc, glycerin and water, the condition completely cleared. The soldier was advised to wear long-sleeved underclothes for protection, and, if necessary, two undershirts. This soldier was returned to duty.



Fig. 23. Case 23. Dermatitis from bichloride of mercury solution used in a case of pediculosis. Note marked edema of scrotum. Itching was intense.

*Case 16.*—A twenty-two-year-old white soldier was admitted to Oliver General Hospital 18 September 1943 with a dermatitis involving both feet. In eighteen months of service, this was his fourth admission to an army hospital. His most recent admission was at Daniel Field Station Hospital 10 July, 1943, where he remained for approximately seven weeks prior to his admission here. This patient had had various medications applied to his feet, including a five per cent solution of alum, gentian violet, and Castellani's solution, and a heat lamp was used. In addition, he heard about the use of camphor-phenol eutexia in the treatment of athlete's foot, and he used it, thinking it would cure his condition, since it was his impression that he had a severe case of athlete's foot.

Contact and allergic history was negative except for a history of athlete's foot of four years duration. The remainder of his past history was negative.

Physical examination, except for his dermatitis, was essentially negative. Over the skin of both feet, involving the big toe and especially the second and third toes, bilaterally, and over the insteps of his feet, occurred a marked amount of crusting, "oozing," vesiculation, papules and pustules with a moderate amount of pigmentation. The lesions about his toes were of a more acute nature, since they appeared to be planted upon an acute erythematous base. From his history, it was apparent that this was where he had applied the camphor-phenol medication.

Laboratory examinations, including complete blood studies, serological tests and urinalysis, were essentially negative. Smears from the skin lesions on several occasions showed no fungi.

Trichophytin reaction by intradermal and patch tests was negative. However, he reacted very markedly to a piece of leather from his GI shoes as well as to

## CONTACT DERMATITIS—RUDOLPH

a 0.005 solution of sodium dichromate. It was our impression that we were dealing with a contact dermatitis due to leather, upon which was superimposed a dermatitis produced by camphor-phenol. Trichophytosis was ruled out by the absence of any fungi between the toes. Local treatment consisted of soaks of

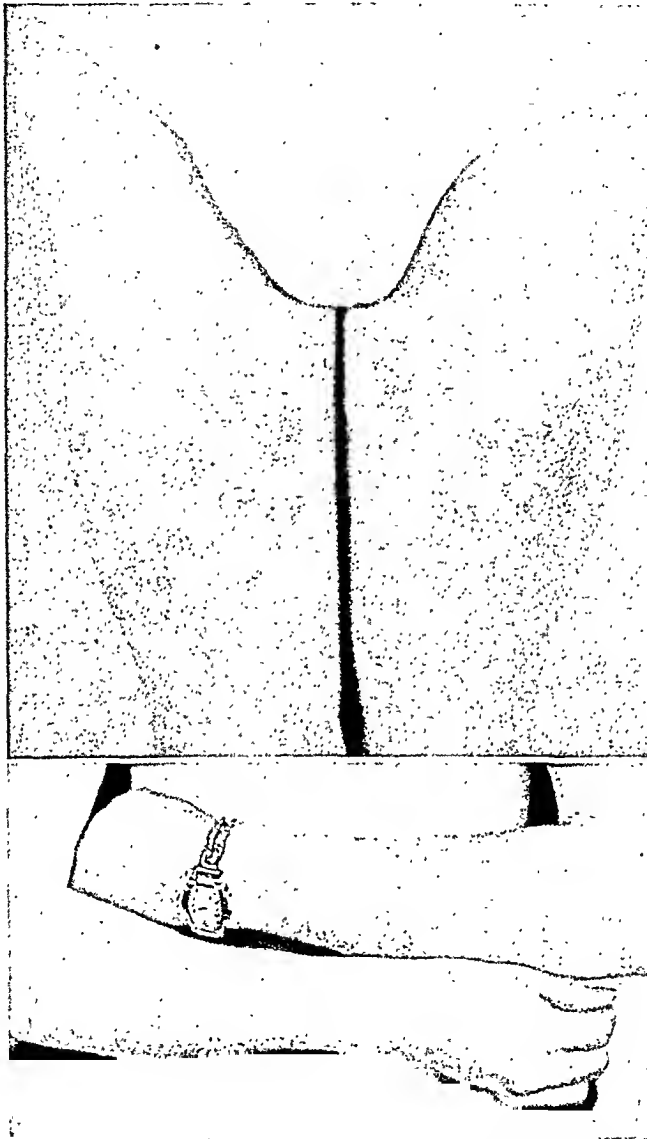


Fig. 24. Case 24. Contact dermatitis, due to wool and O.D. wool clothing, as proved by patch tests to a segment of the patient's own wool clothing and a patch of undyed wool.

potassium permanganate, 1-5000 solutions, three times daily for one week, followed by twice daily soaks of boric acid and alum solution for five days, after which no therapy was used. The condition of his feet cleared and a trial at wearing his GI shoes was made. Within twenty-four hours, he developed marked itching

and vesiculation on the insteps of his feet, which subsided after the avoidance of wearing the shoes. The wearing of low-quartered shoes resulted in less discomfort, but did not completely eliminate the condition. It was felt that separation from the service in this case was indicated, and it was accomplished.

Since this article was originally written, antibiotics such as penicillin, streptomycin and others to come are being widely used at the present moment in the treatment of numerous diseases, both parenterally and locally. Contact with the antibiotics whether because of treatment or through the handling of such material, has caused moderate to severe reactions on the skin as illustrated by the reports of Robinson and Wallace<sup>27</sup>, Johnson<sup>17</sup>, Pyle and Rattner<sup>25</sup>, Raper and Coghill<sup>26</sup>, and McGuire.<sup>20</sup> Nurses, technicians, corpsmen and WACs have had reactions on their extremities and face following the preparation of penicillin for treatment purposes. In some of these individuals, their reactions have occurred within six to eight hours after contact with penicillin.

Capt. Lawrence C. Goldberg<sup>12</sup>, Chief of Dermatology at Oliver General Hospital, stated that, in his experience, "some 6 to 8 per cent of the individuals treated with topical applications of penicillin, where 800 units of penicillin was used per gram of vehicle, demonstrated mild to severe local reactions. Sixteen cases of dermatitis venenata caused by penicillin or its impurities have been proven by patch tests. Occasionally the parenteral or local use of penicillin in the treatment of skin diseases will produce a localized Herxheimer reaction, which must be differentiated from a contact dermatitis. This type of reaction usually subsides within forty-eight hours and appears to be the result of impurities rather than the penicillin itself." The sites of predilection for contact dermatitis from penicillin when caused by the preparation of the drug may be on other portions of the body other than the fingers and hands so that it should be suspected in medical attendants and workers who complain of facial pruritus and orbicular edema.

A clinical example of penicillin dermatitis is described.

B. F., 2nd Lt., ANC, appeared in consultation at the Dermatology Out Patient Clinic on 15 December 1945 because of erythema and edema of the right eyelid associated with erythematous macules on the face. Pinhead sized vesicles were present on the forehead, nose, and perioral areas. She stated that itching and swelling of the face first was noticed on 10 December, 1945. A diagnosis of contact dermatitis was made and the patient was hospitalized. In three days after local treatment with cold wet dressings of Burow's solution, the eruption and the edema subsided and the patient was returned to duty. At that time, the cause of the dermatitis was unknown. Within forty-eight hours, the patient reappeared for consultation because of severe edema of the eyelids, nose, and lips and a recurrent erythema of the face. It was learned that during this time she had been preparing and administering intramuscular injections of penicillin in 20,000 units per c.c. quantities and it appeared that after each injection given to a patient, itching and edema of her face increased. She was again relieved of duty and hospitalized. Treatment as before cleared the condition within three to four days. A patch test with penicillin, 250 units per c.c., was made on the flexor surface of the right forearm and within

## CONTACT DERMATITIS—RUDOLPH

forty-eight hours a 3 plus reaction was noted. After a ten-day leave, the patient returned to duty and a test dose of penicillin was prepared, 250 units per c.c., and injected into a patient. Shortly thereafter, slight swelling and itching of the eyelids and face were noted.

The interesting observation on this particular patient was the fact that the entire contact dermatitis appeared on the face but never involved the extremities or any other portion of the body. In many respects, this type of reaction is similar to that seen in nail polish dermatitis.

### SUMMARY

The use of the term contact dermatitis in this paper has been broadly interpreted and includes that group of acute or chronic inflammatory reactions in the skin, often called dermatitis venenata, eczematous dermatitis, or just eczema. It is a type of dermatitis involving chiefly the epidermis and is the result of contact with external agents. It is characterized by a vesicular eruption on the exposed surfaces of the skin at the outset of the dermatitis.

Contact dermatitis is a frequent cause of morbidity in the army, because it is known to be more common in adult males, who are more likely to be exposed to contact with external irritants. The contactants which may produce contact dermatitis are legion—they may be drugs, clothing, dyes, metals, chemicals, paints, lacquers, or they may be cosmetics (orris root), insect powders (pyrethrum) or many other items. They may be plants, such as poison ivy, oak, sumac, anacardiacea, timothy, or ragweed. In these instances the contactant is an oleoresinous substance present in the leaf of the plant or in the pollen. From a clinical-pathological standpoint, the eruption occurs after a period of previous exposure to the irritant. This contact may occur with large quantities of the excitant, causing symptoms. Once the sensitivity has been produced, however, contact dermatitis may result from infinitesimal amounts. The location of the dermatitis is of diagnostic significance, since it may point to the possible cause. Diagnosis is further aided by a careful history. Final proof of the cause is established by the patch test which requires proper interpretation. Cure will depend on complete removal of the contact and the disappearance of the eruption, except when complicating secondary infection is present.

Pathologically, the anatomic lesion of contact dermatitis is an edema of the epidermis, which is responsible for the typical vesicle. Since this is the result of specific sensitivity in the superficial layer of skin, the necessity for placing the excitant to be tested in direct contact with the skin is thus explained.

Since the lesions of contact dermatitis generally involve the exposed surfaces of the body as a result of contact with external excitants, the presence of vesicles and the absence of a personal or family history of atopy

make the differential diagnosis of contact dermatitis from atopic eczema fairly definite.

The treatment and disposition of contact dermatitis depend upon finding the specific cause. If this has been accurately determined, the only effective cure is, in most cases, the avoidance of contact. This is not always practical in the case of soldiers sensitive to their uniforms or shoes. In some instances, protection can be had by the use of long underwear, but this may not be adequate to avoid skin reactions. Desensitization cannot be carried out against many chemicals and articles of clothing in the army where avoidance cannot be practiced, so that the only expedient thing to do, in many cases, both from the standpoint of the government and the patient, is separation from the service.

Specific desensitization can be used with success only in types of dermatitis produced by plants and pollens, as for example, poison ivy plant and ragweed pollen. Treatment may be administered as prophylaxis or in active treatment when the attack of plant or pollen dermatitis has occurred.

Finally, it must be remembered that we are frequently dealing with an uncomfortable patient who requires relief, so that local applications of soothing, aqueous, anti-pruritic and mildly astringent lotions should be employed in the acute cases. Ointments, X-ray and ultraviolet light therapy may be beneficial in the chronic types as palliative measures. Vaccines, histamine or other non-specific measures are of less value in dermatitis due to contact than in the atopic dermatoses.

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(Continued on Page 141)

# P R E L I M I N A R Y   P R O G R A M

Annual Meeting

## *American College of Allergists*

June 28-30, 1946

Clift Hotel

San Francisco, California

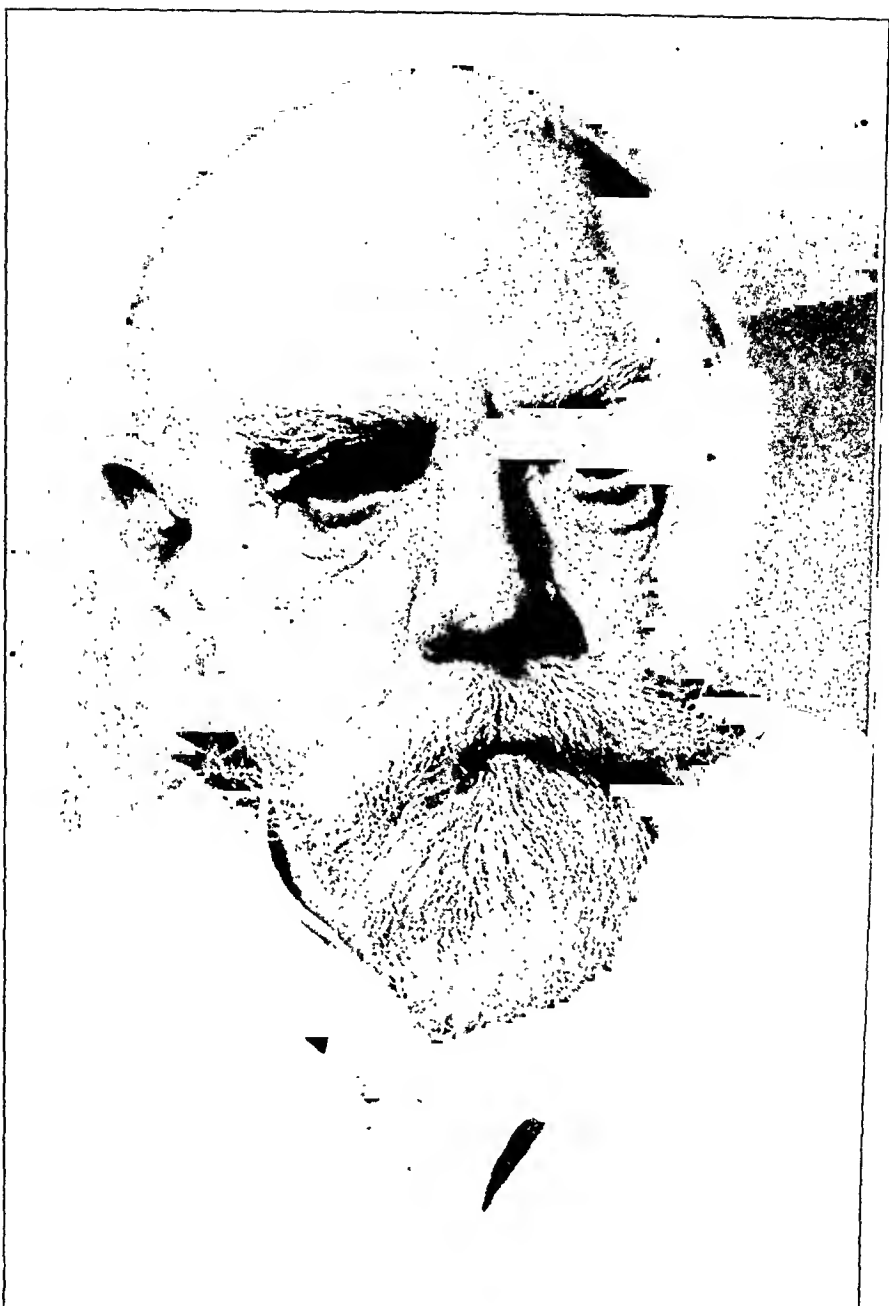
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96th Annual Meeting, American Medical Association, St. Francis Hotel,  
San Francisco, July 1-5, 1946.

12th Annual Meeting, American College of Chest Physicians, Hotel Sir  
Francis Drake, San Francisco, June 27-30, 1946.

NOTE: The papers will not necessarily be presented in the order indicated in this preliminary program and the titles of the papers and authors are subject to change.



Photograph by Claire Roessiger, Basel

ROBERT DOERR, M.D., Ph.D.

*Professor Emeritus of Hygiene and Bacteriology at the  
University of Basel, Switzerland*

Guest Speaker, 1946

# Preliminary Program

Friday, June 28, 1946

## Breakfast

*Clift Hotel—7:30 to 8:30 a.m.*

Members of Board of Regents and Program Committee

## Registration

*Roof Lounge—8:00 a.m.*

## Morning Session

*Roof Lounge—9:00 a.m.*

RUDOLF L. BAER, M.D., *Chairman*

- Experimental Sensitization and Antihistaminic Substances—R. L. MAYER, M.D., Summit, New Jersey  
Evaluation of Intramuscular Injections of Poison Ivy Extract for the Treatment of Acute Rhus Dermatitis—J. B. HOWELL, M.D., Dallas, Texas  
Contact Testing of the Buccal Mucous Membrane with Special Reference to Penicillin—LEON GOLDMAN, M.D., Cincinnati, Ohio.  
Urticaria Due to Handling of Penicillin and Sulfu Drugs—KATHARINE BAYLIS MACINNIS, M.D., Columbia, South Carolina  
Relationship of Antihistaminic Drugs to Other Forms of Therapy in Nasal Allergy and Asthma—ALBERT V. STOEßER, M.D., Minneapolis, Minnesota  
Benadryl in the Treatment of Certain of the Allergic Diseases of Childhood—GEORGE B. LOGAN, M.D., Rochester, Minnesota  
Food Allergy: A Clinical Problem—ORVAL R. WITHERS, M.D., Kansas City, Missouri

## College Luncheon

*Clift Hotel—12:30 to 2:00 p.m.*

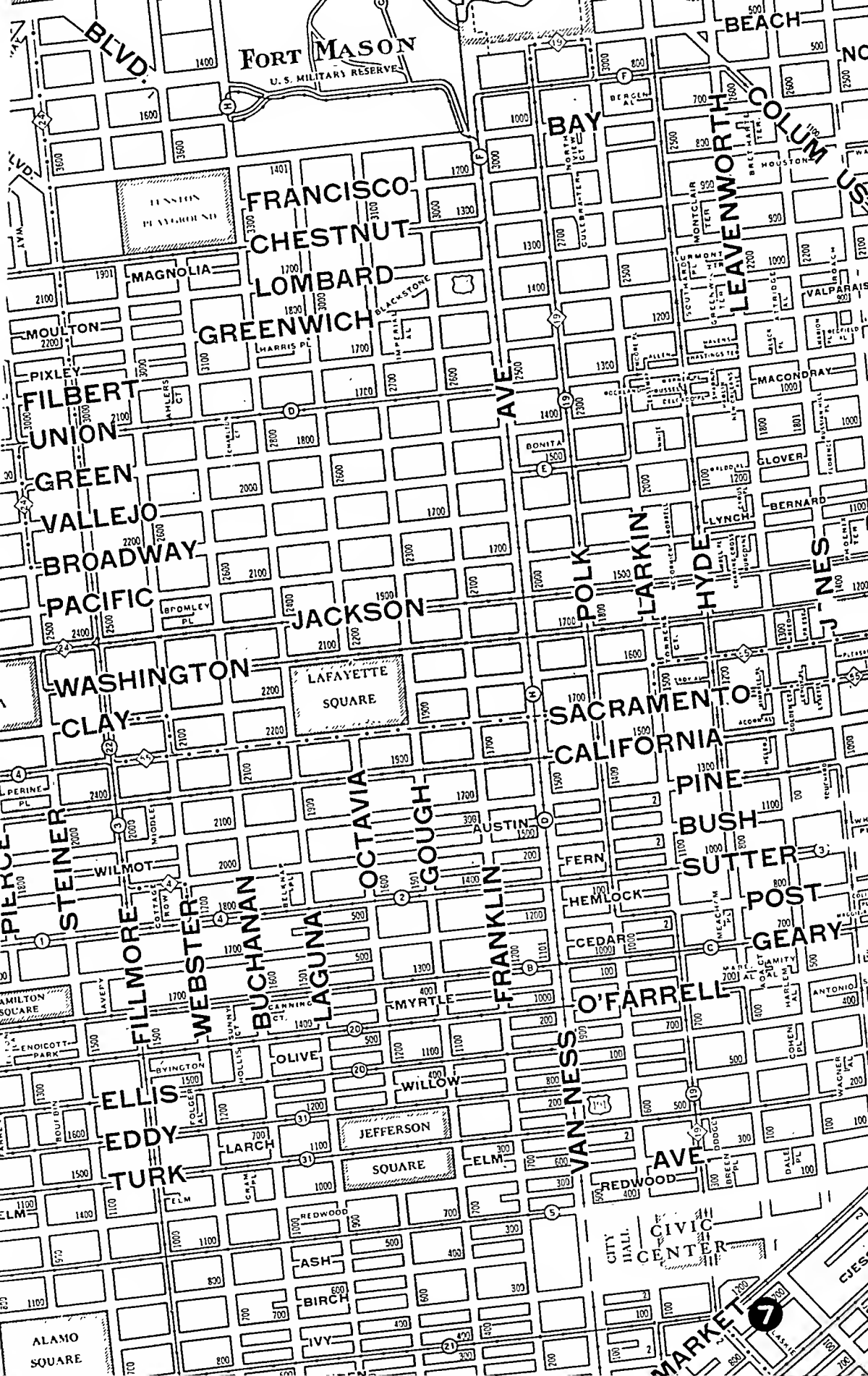
## Afternoon Session

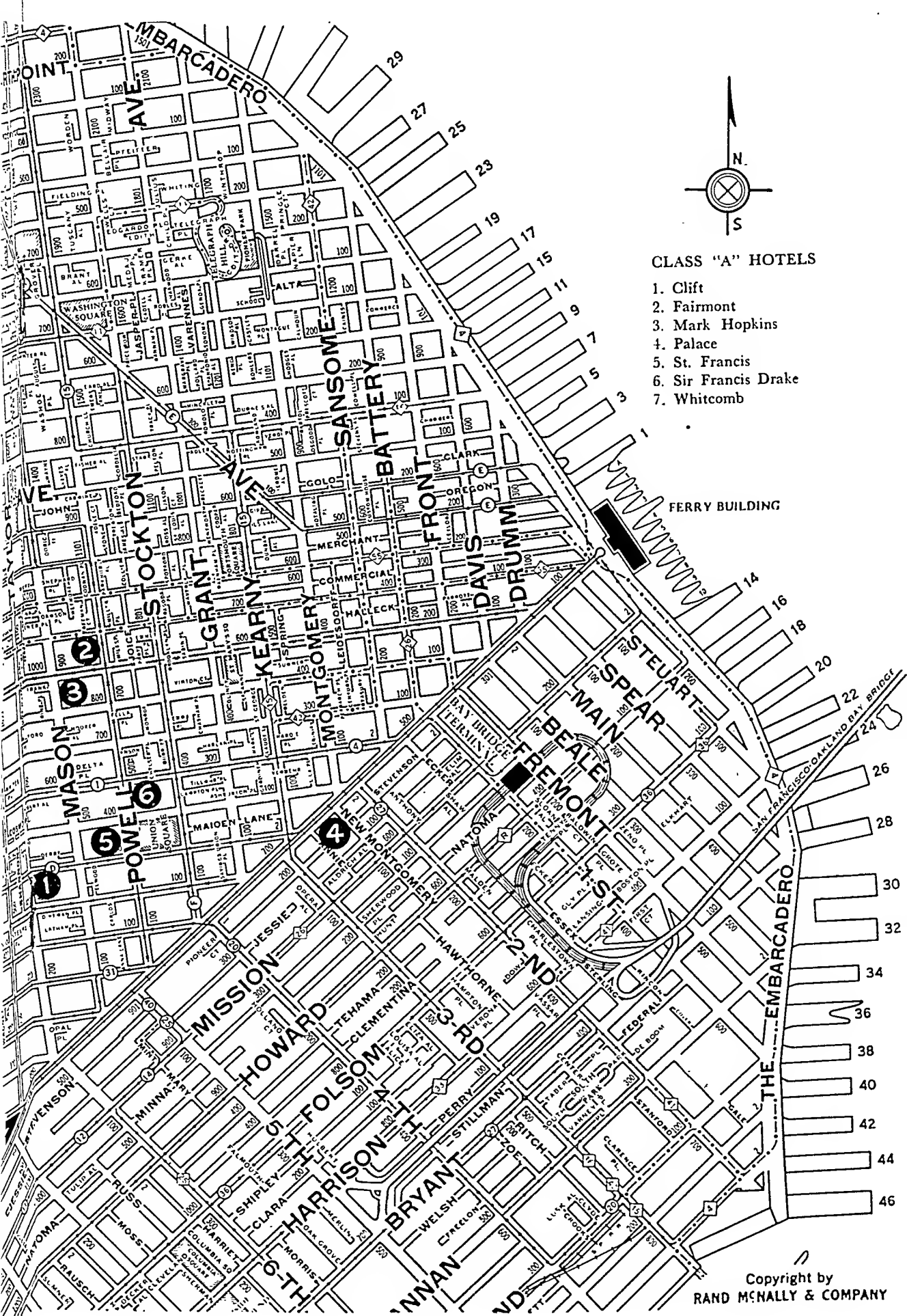
*Roof Lounge—2:00 p.m.*

## PAN-AMERICAN CONGRESS ON ALLERGY INTERNATIONAL ASSOCIATION OF ALLERGISTS

FRED W. WITTICH, M.D., *Chairman*

- Introduction of ROBERT DOERR, M.D., Ph.D., Basel, Switzerland, Guest Speaker Saturday morning session.  
Opening Address, "Terminology and Classification of Allergy"—GUIDO RUIZ-MORENO, Buenos Aires, Argentina; Argentine Allergy Society  
The Influence of the Liver on Anaphylactic Shock in the Dog—ALFONSO GRAÑA, M.D., Montevideo, Uruguay  
Topic to be announced—G. ESTRADA DE LA RIVA, M.D., Havana, Cuba  
Topic to be announced—FRANCISCO J. FARRERONS, M.D., Barcelona, Spain  
Topic to be announced—MARIO MIRANDA, M.D., NELSON PASSARELLI, M.D., Rio de Janeiro, Brazil.  
Topic to be announced—Representative from Canada  
Clinical and Physical Nature of Pollen Allergens—HAROLD ABRAMSON, M.D., New York, N. Y.





CLASS "A" HOTELS

1. Clift
2. Fairmont
3. Mark Hopkins
4. Palace
5. St. Francis
6. Sir Francis Drake
7. Whitcomb

## PRELIMINARY PROGRAM

### Evening Session

*Roof Lounge—8:00 p.m.*

## THE ASSOCIATION OF ALLERGISTS FOR MYCOLOGICAL INVESTIGATION

### Symposium on Mold Allergy

HOMER E. PRINCE, M.D., Houston, Texas, *Director*

Mold Allergy in West Texas—

Clinical Observations

ERLE D. SELLERS, M.D.

Discussion opened by: ORVAL WITHERS, M.D., Kansas City, Missouri

Mold Fungi in the Etiology of Respiratory Allergic Disease

A Survey of Air-borne Fungi in the San Antonio Area, and a Correlation with Skin Reactions to Mold Extract

STANLEY F. HAMPTON, M.D.

Discussion opened by: PEARL ZINK, M.D., San Antonio, Texas

Mold Fungi in the Etiology of Respiratory Allergic Disease:

Further Survey Studies in Various Cities

MARIE B. MORROW, Ph.D., Austin, Texas

Discussion opened by: MERLE MOORE, M.D., Portland, Oregon

Intrinsic Fungus Problems in Relation to Asthma and Bronchitis:

L. O. DUTTON, M.D., El Paso, Texas

Discussion opened by: FRED WITTICH, M.D., Minneapolis, Minnesota.

**Saturday, June 29, 1946**

### Breakfast

*Clift Hotel—7:30 to 8:30 a.m.*

Members of Board of Regents and Program Committee

### Registration

*Roof Lounge—8:00 a.m.*

### Morning Session

*Roof Lounge—9:00 a.m.*

HARRY L. ROGERS, M.D., *Chairman*

Address of the Guest of Honor—Integration and Differentiation of Allergic Phenomena—ROBERT DOERR, M.D., Ph.D., Professor Emeritus of Hygiene and Bacteriology at the University of Basel, Switzerland.

Reagins: Preliminary Report on Experimental Evidence in Support of a New Theory of their Nature—HYMAN MILLER, M.D., Beverly Hills, California, and DAN CAMPBELL, Ph.D., California Institute of Technology

Food Allergy in Dogs—RALPH POVAR, M.D., Rhode Island

Contact Dermatitis in the Horse—LESTER REDDIN, JR., V.M.D., Pearl River, N. Y.

Allergy and Immunity to Crystalline Insulin—MARY H. LOVELESS, M.D., New York, N. Y.

Quantitative Relationships in Anaphylaxis and Allergy—ALFRED J. WEIL, M.D., Pearl River, N. Y.

Inhalant Allergens in Southern California—WILLARD S. SMALL, M.D., Pasadena, California

### College Luncheon

*Clift Hotel—12:30 to 2:00 p.m.*

## PRELIMINARY PROGRAM

### Afternoon Session

*Roof Lounge—2:00 p.m.*

MERLE W. MOORE, M.D., *Chairman*

Aerosol Therapy of the Lungs and Bronchi—HAROLD ABRAMSON, M.D., New York, N. Y.

Recent Developments in the Treatment of Intractable Bronchial Asthma (including moving picture demonstrations)—ALVAN L. BARACH, M.D., New York, N. Y.

Mistakes in the Treatment of Asthma—GEORGE WALDBOTT, M.D., Detroit, Michigan

Continuous Intravenous Aminophyllin Therapy in Status Asthmaticus—ROBERT J. GOODALL, M.D., Chicago, Illinois and LEON UNGER, M.D., Chicago, Illinois

Grass Pollen Counts of the Los Angeles Area—A. M. TARGOW, M.D., Los Angeles, California

Allergenic Potency of Pollen Extracts: Technical Considerations—ROGER P. WODEHOUSE, Ph.D., Pearl River, N. Y.

Respiratory Mold Allergy—A Twelve Months' Atmospheric Survey in San Francisco—WILLIAM C. DEAMER, M.D., San Francisco, California

### Cocktail Hour

*Clift Hotel—6:15 p.m. to 7:15 p.m.*

Presented through the courtesy of  
Frederick Stearns and Company, Detroit, Michigan

### Informal Dinner

*Clift Hotel—7:15 p.m.*

## Sunday, June 30, 1946

### Breakfast

*Clift Hotel—7:30 to 8:30 a.m.*

Members of the Board of Regents and Program Committee

### Registration

*Roof Lounge—8:00 a.m.*

### Morning Session

*Roof Lounge—9:00 a.m.*

FRENCH K. HANSEL, M.D., *Chairman*

Some Properties of Antigens and Antibodies—SANFORD B. HOOKER, M.D., Boston, Massachusetts

Application of Peroxide Solutions to Allergic Syndromes—ETHAN ALLAN BROWN, M.D., Boston, Massachusetts

Use of the Sex Hormones in Allergic Disorders—MILTON M. HARTMAN, M.D., San Francisco, California

Histamine and Deafness—BAYARD T. HORTON, M.D., and OLAV E. HALLBERG, M.D., Rochester, Minnesota

Psychoanalysis and Psychosomatic Allergy—COYNE H. CAMPBELL, M.D., Oklahoma City, Oklahoma

## PRELIMINARY PROGRAM

### College Luncheon

*Clift Hotel—12:30 to 2:00 p.m.*

### Afternoon Session

*Roof Lounge—2:00 p.m.*

HAL DAVISON, M.D., *Chairman*

Vascular Allergy—JOSEPH HARKAVY, M.D., New York, N. Y.

3:30 p.m.—Presidential Address—HARRY L. ROGERS, M.D., Philadelphia, Pa.

4:00 p.m.—Annual Business Meeting.



## Important Announcement

There will be a meeting of the Board of Regents of the College, Thursday, 2:00 P.M., June 27, at the Clift Hotel, San Francisco.

There will also be an important meeting of the Standardization Committee, Thursday evening, June 27, at 8:15 P.M., at the Clift Hotel. See Page x for those on this Committee. All members of the Board of Regents are also urged to attend.

## HOTEL RESERVATION APPLICATION

AMERICAN COLLEGE OF ALLERGISTS

Meeting, June 28-30, 1946

Headquarters—Clift Hotel

**If you are staying through both meetings of your Society and the AMA fill out both applications on this page.**

**Note :** Single rooms are *very limited* in number. Please arrange to *share* twin-bedded rooms. Be sure to give five choices of hotels.

Mr. M. Laurence Montgomery, Chairman  
Sub-Committee on Hotels,  
American Medical Association Convention,  
Rm. 200 Civic Auditorium,  
San Francisco 2, Calif.

I shall attend the meeting of the American College of Allergists, June 28-30, 1946.  
Please reserve the following:

1st Choice.....Hotel ...Room(s) for....person(s) Rate \$..... to \$.....

2nd Choice.....Hotel ...Room(s) for....person(s) Rate \$..... to \$.....  
(Twin Bedded Rooms)

3rd Choice.....Hotel ....Room(s) for....person(s) Rate \$..... to \$.....  
(Double Bedded Rooms)

4th Choice.....Hotel ...Suite(s) for.... person(s) Rate \$..... to \$.....  
(Parlour Bedroom and Bath

5th Choice.....Hotel OR Two Bedrooms with Bath Between)

## ARRIVING SAN FRANCISCO

Date : .....

Hour.....A.M.....P.M. DEPARTURE DATE: .....

ROOMS WILL BE OCCUPIED BY:

NAME	ADDRESS	CITY	STATE
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Persons attending ONLY PRE-AMA CONVENTION MEETINGS MUST VACATE ROOMS NO LATER THAN THE CHECK-OUT HOUR, MONDAY, JULY 1, 1946. This is mandatory so that Doctors attending the AMA Convention may secure reservations.

APPLICATION FOR RESERVATION FOR THE AMERICAN MEDICAL ASSOCIATION CONVENTION, JULY 1-5, 1946

Please reserve the same room(s) as on page 1..... (Mark with check)

.....Room(s) for.....person(s) Rate \$..... to \$.....

.....Room(s) for.....person(s) Rate \$..... to \$.....  
(Twin Bedded Room(s))

.....Room(s) for.....person(s) Rate \$..... to \$.....  
(Double Bedded Room(s))

.....Suite(s) for.....person(s) Rate \$..... to \$.....  
(Parlour Bedroom & Bath OR Two Bedrooms, Bath Between)

ROOMS WILL BE OCCUPIED BY: (Same as page 1.....Mark with check)  
OR

NAME	ADDRESS	CITY	STATE
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NOTE: The Housing Committee of the AMA will delay confirmation of reservation until after May 15, in order more accurately to judge the total load, and if possible accommodate those doctors who wish to bring families and guests.

## RATES—SAN FRANCISCO HOTELS

### MEMBERS OF THE SAN FRANCISCO CONVENTION AND TOURIST BUREAU

CLASS "A"	SINGLE	DOUBLE	TWIN
Clift .....	\$4.00 to \$6.00	\$6.00 to \$ 8.00	\$7.00 to \$10.00
Geary at Taylor			
Fairmont .....	4.00 to 8.00	6.00 to 12.00	7.00 to 12.00
950 Mason			
Mark Hopkins .....	5.00 to 8.00	7.00 to 10.00	7.00 to 12.00
999 California			
Palace .....	4.00 to 7.00	6.00 to 10.00	7.00 to 10.00
Market & New Montgomery			
St. Francis .....	4.00 to 8.00	6.00 to 10.00	7.00 to 12.00
Powell & Geary			
Sir Francis Drake .....	4.00 to 7.00	6.00 to 9.00	7.00 to 10.00
Sutter & Powell Sts.			
Whitcomb .....	3.00 up	4.00 to 7.00	4.00 to 7.00
1231 Market St.		2 room suite	9.00 to 12.00
CLASS "B"	SINGLE	DOUBLE	TWIN
Alexander Hamilton .....	3.00 to 5.00	4.00 to 6.00	4.50 to 7.00
620 O'Farrell			
Bellevue .....	3.00 to 4.00	4.00 to 5.00	4.50 to 6.00
Geary & Taylor			
Californian .....	2.50 to 3.00	3.50 to 4.50	4.00 to 4.50
405 Taylor			
Canterbury .....	2.50 to 3.00	3.50 to 4.50	4.00 to 6.00
750 Sutter			
Chancellor .....	2.50 to 3.00	3.50 to 4.00	4.00 to 4.50
433 Powell			
Drake-Wilshire .....	2.00 to 3.00	3.00 to 4.00	4.50 to 5.00
340 Stockton			
Embassy .....	2.25	2.75	3.50
610 Polk St.			
Gaylord .....	2.50 to 3.00	3.50 to 5.00	4.00 to 5.00
620 Jones			
Manx .....	2.50 to 3.00	3.50 to 4.00	5.00
225 Powell			
Maurice .....	2.50 to 3.50	3.50 to 5.00	4.50 to 5.00
761 Post			
Plaza .....	3.00 to 4.00	4.00 to 5.00	4.50 to 6.50
Post & Stockton			
Stewart .....	2.00 to 2.50	3.00 to 4.50	4.00 to 6.00
353 Geary			

# RATES—SAN FRANCISCO HOTELS

CLASS "C"	SINGLE	DOUBLE	TWIN
Ambassador ..... 55 Mason St.		2.50 to 3.00	3.50 to 4.00
Biltmore ..... 735 Taylor St.	2.00	2.50	3.00
Brayton ..... 50 Turk St.	2.00 to 2.50	2.50 to 3.00	4.00
Carlton ..... 1075 Sutter St.	2.50	3.00 to 3.50	3.50 to 4.50
Cecil ..... 545 Post St.	2.00 to 2.50	3.00 to 3.50	3.50 to 4.00
Colonial ..... 650 Bush St.	2.25 to 2.50	3.00 to 3.50	4.00
Continental ..... 127 Ellis St.	1.50	2.00 to 3.00	3.00 to 3.50
Court ..... 555 Bush St.	1.50	2.50	3.75
Edison ..... 1540 Ellis St.	1.50	2.00 up	3.00 up
Federal ..... 1087 Market	1.25 to 2.25	1.75 to 2.75	2.50 to 3.50
Fielding ..... Geary & Mason	2.50 to 3.50	3.50 to 4.50	4.00 to 6.00
Golden State ..... 114 Powell	1.50 to 2.50	2.00 to 3.50	3.50 to 5.00
Granada ..... 1000 Sutter St.	1.00 to 1.50	2.00 to 3.50	3.00 to 3.50
Grand Hotel ..... 57 Taylor	2.00 to 3.00 Weekly 1 day off bill	2.50 to 3.50 Monthly 25% off bill.	
Keystone ..... 54 Fourth St.	1.25 to 1.50	2.00 to 2.50	3.50
La Salle ..... 225 Hyde St.	2.00 to 3.00	2.50 to 3.50	4.00
Mark Twain ..... 345 Taylor	2.00 to 2.50	2.50 to 3.50	4.00
New Alden ..... 333 Fulton	1.50 to 2.00	2.00 to 2.50	3.50
Olympic Hotel ..... 230 Eddy	2.00 to 3.00	2.50 to 3.50	3.50 to 4.00
Oxford ..... Market & Mason	2.00 to 3.00	3.00 to 3.50	4.00
Powell ..... 17 Powell	2.00 to 2.50	2.50 to 3.00	3.00 to 3.50
Roosevelt ..... Jones & Eddy	2.50	2.50 to 3.00	3.00 to 4.00
Senate ..... 467 Turk St.	1.50 to 2.00	2.50 to 3.00	3.00 to 4.00
Senator ..... 619 Ellis St.	1.50 to 2.50	2.00 to 3.00	3.00 to 4.00
Shaw ..... Market & McAllister		3.50 to 4.00	4.00 to 5.00
States ..... 556 California	1.10 to 1.65	2.50	
Victoria ..... 590 Bush	2.00 to 2.50	3.00	3.50
Washington ..... Grant Ave. at Bush	2.00 to 2.50	2.50 to 3.00	4.00
Worth ..... 641 Post	2.00 to 2.50	2.50 to 3.00	3.50

## APARTMENTS

Alexander Hamilton ..... 6.00 to 16.00

## MOTELS

Marina Motel ..... 2.50 to 4.00 per day 16.50 to 24.00 per week

# ANTIGENICITY OF PROTEINS IN RELATION TO ALLERGY

WILLIAM H. WELKER, Ph.D., Sc.D.

Chicago, Illinois

I appreciate the invitation to speak before this group. It must be understood, however, my interests do not lie in the field of allergy from the standpoint of the practice of allergy. I have been interested for many years in the chemistry of proteins and through my collaboration with Dr. Hektoen I became interested in their immunologic reactions. I wish to acknowledge my indebtedness to Dr. Hektoen for the development of my appreciation of this angle of the protein knowledge. I also wish to acknowledge my indebtedness to many young medical students whose scientific curiosity stimulated them to carry out work which supplied much of the information that we have on this subject at the present time.

The immunology of proteins is today much confused because most of our present information has been secured with mixtures of antigens, such as blood sera, bacterial filtrates and other material of the same type. Such mixtures contain many antigenic entities, diversified in character and as a result the interpretation of their effects is beyond the capacity of the human mind.

Twenty years ago, in his book on *The Chemical Aspects of Immunity*, Wells<sup>14</sup> made the following statement (he is speaking about the results obtained on protein cleavage products): "These are variable preparations concerning the source, composition, and the purity of which the observer has no knowledge. To call work done with such materials scientific investigation is in my conviction a prostitution of the word science, a parody of its standards and ideals." This statement in my judgment applies with equal force to the use of mixtures of antigens, known and unknown, in studies to establish antigenic effect. Later in his text he makes the following statements in italics: "The fundamental processes of immunity should be studied only with the simple antigens of known composition, i.e., isolated pure protein."<sup>14</sup> For those who are interested in the fundamental science I would recommend the reading and study of this book.

When we study the antigenicity of a protein we shall have to take into consideration not only the reactivity of the protein itself, but also the reactivity of the species. Not all species have the ability to react with proteins that are known to be highly antigenic to some species. In our present state of knowledge we know of three classes of antigens. These groups differ from the chemical standpoint in size of the molecule and

<sup>14</sup>From the Department of Biological Chemistry, University of Illinois, College of Medicine, Chicago, Illinois. Delivered at the dinner given by the American College of Allergists, at the instructional course held in Chicago, Illinois, November 5, 1945.

from the physical-chemical standpoint in the size of the particle in solution. The response of the reactive animal organism is different in the case of each of these groups. It is my belief that the difference in the response to these three classes of antigens is due largely to the particle size of the protein when in solution. In all probability, different cells of the animal organism are called upon to handle them when they appear in the blood stream and the different groups of cells have their own characteristic methods for handling the situation.

When diluted egg white (1 per cent protein in physiological salt) is injected into the blood stream of the dog, the reticulo-endothelial system becomes engorged with the large particles and relatively small doses will cause death.<sup>12</sup> If these same proteins are injected in a more highly dispersed solution, the kidney can handle large quantities of them readily.

The first group of antigens consists of antigenic proteins of relatively large molecular size. An example of this group is ovalbumin. When these proteins get into the blood stream of a responsive animal they will cause the production of antibodies of the type of precipitins, agglutinins, lysins, et cetera. They also have the power of producing anaphylactic sensitivity. It has been unfortunate for the progress of our basic conceptions in allergy that our train of thought has been developed along the lines of anaphylaxis or anaphylactic sensitization. This type of antigen does not readily produce a response in the human organism. If it did, the use of antitoxins would become extremely hazardous. There is the possibility that the human organism may develop anaphylactic sensitivity to the pseudoglobulin of the horse which is the main constituent in diphtheria and tetanus antitoxin, but such development is so rare that there are few practicing physicians who make use of any precautionary methods in connection with the use of these two antitoxins.

C. W. Wells<sup>13</sup> studied the blood of diphtheria patients who had been treated with whole horse serum diphtheria antitoxin. Out of 26 cases studied one showed a titer of over 1-40,000, four over 1-20,000 and one over 1-10,000, the rest inconsequential or negative. Tuft and Ramsdell<sup>10,11</sup> carried out work along the same lines on the human subject and found even less response. Coca<sup>5</sup> used normal subjects and normal horse serum and obtained negative results.

The rabbit and guinea pig show a very high degree of response to this class of antigens. A precipitin titer of 1-100,000 or 1-1,000,000 is common. When the human organism is in a pathological state, conditions may exist which favor the formation of precipitins to an antigenic protein. After the epidemic of typhoid fever at Manteno, Spinka<sup>12</sup> studied the blood of all the recovered cases and found that all of them had high precipitin titers for the characteristic protein of the typhoid organism. The diphtheria cases studied by C. W. Wells were all in a toxic state due to the fact that they were suffering from diphtheria which may account

for the response obtained in his series. Tuft and Ramsdell used individuals that were treated with antisera for specific infections and the few positive responses that were observed by them can well have been due to the conditions produced by the pathologic state.

Coca used normal individuals and normal horse serum and obtained negative results. He interpreted his results as due to the fact that he had used normal horse serum while Tuft and Ramsdell had used anti-toxin horse serum. I am inclined to believe that the differences in the results obtained were due to the fact that Tuft and Ramsdell had used sick individuals while Coca's subjects were normal. This is further borne out by Burky's<sup>3</sup> experiments on the production of sensitivity to the lens protein of the rabbit in the rabbit. This sensitivity could not be produced without the simultaneous injection of staphylococcus toxin. The generally accepted explanation of these results is that the toxin forms a compound with the lens protein and the sensitivity is produced by the foreign protein compound so formed. It might be possible, however, that the toxic condition produced in the rabbit favored the precipitin formation. In the dog, L. Mann and Welker<sup>12</sup> and other investigators have been unable to induce any precipitin formation for antigenic proteins injected. The staphylococcus toxin will not aid in the precipitin formation in this species. It should however, combine with the antigen and thus favor precipitin formation. It also fails to produce any toxicity in the dog. Toxic conditions produced by other means make it possible to produce precipitins in the dog.

An antigenic large protein molecule in animals that have the ability to respond will produce precipitins. In species that normally do not produce these antibodies, the antigenic large protein molecule may produce precipitins under abnormal conditions. These antigenic large protein molecules apparently do not have the power of producing any skin reactivity. A human case of egg sensitivity was studied in the following manner by Aaronson and Cole.<sup>1</sup> The first crystallization of ovalbumin produced a good skin reaction in an egg-sensitive case. Successive crystallization of the same ovalbumin showed diminishing reactions and at the point of the seventh crystallization the skin reaction had disappeared. The precipitinogenic power of this preparation showed no diminution on successive crystallizations. It is, therefore, logical to assume that pure crystallized ovalbumin has no skin reactivity.

The work of Roth and Nelson<sup>9</sup> on pollen, using successive extractions of pollen, showed that after a certain number of extractions all skin reactivity was absent from subsequent extracts. The precipitinogenic power was still present in these later extracts, indicating that the large protein molecule at this point had been freed from the skin reacting substances but its original chemical nature had not been altered. The precipitinogenic power was tested on pollen antisera prepared in the rabbit.

Rappaport and Levin<sup>8</sup> studied this problem by dialyzing a pollen solution against frequent changes of distilled water. They studied the skin reactivity in known pollen-sensitive cases of the solution in the bag on the basis of the nitrogen content and found that the skin reactivity diminished and finally disappeared. They are not entirely satisfied and expect to repeat the work before final publication. The proteins that belong to this group in solution at or near their isoelectric point will not diffuse through permeable membranes.

The next group of antigens consists of proteins of smaller molecular size, typified by the bacterial toxins. These do not form precipitins but form neutralizing antibodies. They will slowly diffuse through permeable membranes and they produce delayed skin reactions. The particle size of the toxin in solution by virtue of its ability to pass through permeable membrane is smaller than that of the particle size of the antigens of the first group.

Here again the question of ability of a given species to respond to the antigens is worth while considering. When it was found that the rabbit produced an antipneumococcus serum that was valuable in the treatment of pneumonia, Dr. Jamieson<sup>7</sup>, Director of the Biological Division of Eli Lilly and Company, studied the ability of the rabbit to produce diphtheria antitoxin. The highest titer obtained in the rabbit after immunization with diphtheria toxin was 4 units per c.c., showing a very marked difference in the degree of responsiveness to this antigen of the rabbit as compared to that of the horse. The preparation of antitoxin antiserum is not practical in the rabbit since the response of this species is feeble to this class of antigens. The pneumococcus antiserum prepared in the horse was of no particular value. The effective agent in the rabbit antipneumococcus serum is the precipitin antibody. The horse is not capable of readily preparing precipitins.

Through the work of Benjamins<sup>2</sup> and his collaborators on grass pollens and of Hecht, Rappaport and Welker<sup>6</sup>, we are introduced to the third group of antigens. This is the group of antigenic substances which I believe is responsible for all forms of allergy. Its particle size in solution is smaller than that of the toxins. It dialyzes readily through a permeable membrane. In nature it occurs partially in combination in form of surface compounds with the larger protein molecule. That is why preparations of the large protein molecule from food and environmental material may show positive skin reactions in sensitized individuals. It is interesting that such small molecules should be as specific as they appear to be. It has been shown that this small molecule can be prepared free from any of the large molecules. This small molecule is exquisitely skin reactive. When completely freed from the large molecule pollen it will not produce precipitins and it will not produce anaphylactic sensitivity. Since this molecule is so small and so readily diffusible, it is apparent that these allergy anti-

gens must be present in the blood stream of all individuals who are exposed to environmental antigens or food allergy antigens. Our old theory of accidental introductions of these antigens into the blood stream as the reason for production of sensitivity is no longer valid.

Through the work of Coca<sup>4</sup>, we now know that those individuals react to the presence of these antigens only because the allergic individual has developed a response called reagin. We know nothing about the conditions under which the reagin develops. The human organisms must have resistance against the development of the reagin, otherwise we should be one hundred per cent allergic. The reagin, according to Coca<sup>5</sup>, is different from the precipitin antibody and also from the anaphylactic sensitizing antibody. The allergy problem deserves study, divorced from concepts that are based on information derived from the use of antigens that are entirely different from those involved in allergy.

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Author's comment: "On first glance the results cited might be interpreted as an indication that penicillium-sensitive persons are definitely safe from allergic reactions to penicillin. However, certain quantitative factors must be considered. A probably safe dose of the penicillium extract would be 1,000 times the minimal amount (0.02 c.c. of 1,000) required to give a skin test. On the other hand, a normal daily therapeutic administration of penicillin would be about 200,000 units, or 20,000 times the maximum dose (0.02 c.c. of 500 units per c.c.) used in our tests. This fact, coupled with the greater likelihood of systemic allergic reactions from intravenous administration, makes it impossible to say at the present time that the probability of allergic reactions can be totally ignored. The answer to this question will be more clear when purer and nonirritating penicillin products will be available or when actual therapeutic doses will be administered to penicillium-sensitive persons. Because also the original source of penicillin is a potent antigen and conceivably at times some of the antigen may be a final contaminant, it is suggested that as an added safeguard every batch of commercial penicillin be tested on known penicillium-sensitive individuals."

## D.H.E.45 (DIHYDROERGOTAMINE) IN THE TREATMENT OF ALLERGIC MIGRAINE

LT. COMDR. NORMAN W. CLEIN, MC, USNR  
Seattle, Washington

**H**HEADACHE represents one of the most common complaints. Although extensive studies have been in progress in an effort to evaluate the causative factors, the patient's chief concern is to seek symptomatic relief from migrainous headache which is so frequently incapacitating.

Many hypotheses have been advanced, but the etiology of migraine still remains unsolved. The mechanism of migraine is believed to be due to a vasoconstriction followed by a vasodilatation of the cerebral arteries. The vasoconstriction produces the aura, scotomata and other phenomena and the vasodilatation produces the headache by stretching the pain fibers closely associated with these arteries. There is disagreement on the trigger mechanism that first causes the vasoconstriction and the vasodilatation that follows. One of the accepted theories is that migraine is an allergic reaction. Von Storch<sup>6</sup> reported a considerable number of migrainous patients as allergic. Rowe<sup>5</sup> reported only 17 per cent failure by the use of elimination diets.

In recent years ergotamine tartrate has been found to be the drug of choice in the treatment of typical migraine. Although the mechanism of action of this drug is still unknown, nevertheless the drug has been found to be useful in aborting headaches due to various causes. Lennox and Von Storch<sup>4</sup> report that 90 per cent of the patients obtained prompt relief when ergotamine was given intravenously or subcutaneously. One of the undesirable features of ergotamine is the production in some cases of nausea, vomiting and precordial pain. However, these side effects can be diminished by giving a minimum effective dose and it can be said that once a headache is relieved by ergotamine, the drug will continue to produce the desired results.

Recently a new drug known as dihydroergotamine (D.H.E.45)\*, an ergotamine derivative, has been placed at my disposal. Each c.c. of D.H.E.45 contains 1 mg. of dihydroergotamine.

Horton, Peters and Blumenthal<sup>2</sup> have reported their experience with this new substance in 120 cases of migraine. In their series, seventy-nine patients showed all the features of typical migraine. Seventy-five per cent of these patients obtained good to excellent results from the use of D.H.E.45. The remaining forty-one patients had a typical migraine and only 36 per cent obtained good to excellent results with D.H.E.45. These workers found that D.H.E.45 was just as effective as

The opinions or assertions contained herein are the private ones of the writer and are not to be construed as official or reflecting the views of the Navy Department.

\*Furnished by Sandoz Chemical Works, Inc.

ergotamine tartrate in relieving acute attacks of headache and they also observed that D.H.E.45 was three times less toxic than ergotamine tartrate.

It is interesting to note that D.H.E.45 possesses a marked sympathetico-paralytic action similar to ergotamine but it exerts no effect on the uterus as contrasted with ergotamine tartrate.

Kirchhof and his associates<sup>3</sup> made observations with D.H.E.45 and epinephrine on the blood pressure of the dog and they found that D.H.E.45 is adrenolytic when subsequent injections of adrenalin are given.

Dannenberg<sup>1</sup> reports his observations with D.H.E.45 on several patients and found it to be as effective as ergotamine tartrate once the nature of the headache is firmly established, and he has found that best results have been obtained if it is used early in a migraine attack.

I have observed the use of D.H.E.45 in twenty-eight patients in whom the symptoms were due to various causes. Twelve of these twenty-eight patients were of unknown etiology after careful physical examination. Nine of these twelve patients obtained no marked relief from the use of D.H.E.45. Three patients were definitely relieved after the use of D.H.E.45 when given subcutaneously.

Sixteen patients had an allergic history plus associated allergic diseases such as chronic allergic rhinitis, asthma or urticaria. They also had more or less typical migraine consisting of unilateral or bilateral pulsating headache, associated with nausea and occasionally with vomiting. Previously they obtained relief only by lying down in a quiet dark room and allowing the symptoms to "wear off" inasmuch as they were not helped by any previous medication. Eleven of these allergic cases were given quicker relief by D.H.E.45 than with any previous medication and the headache generally disappeared in one to three hours. Only one patient experienced some nausea and felt "jittery" from the injection and yet this patient voluntarily returned for another injection when his headaches recurred. One other patient felt slightly nauseated. Several patients had a second injection when the first did not afford relief. In other words, if the first injection did not relieve the headache, the second usually did not.

Fourteen of the patients had from four to eight injections (one only for each attack) whenever the headaches recurred and this was over a period of four months. Two patients had had Gynérgen previously and experienced side effects but after receiving injections of D.H.E.45, the headache was relieved and no side effects occurred.

In addition, all allergic patients with migraine were put on an allergic routine consisting of: (1) diet—eliminating common allergens such as cocoa, nuts, spice, shell fish, pork, juices; (2) environmental control—avoiding dust, odors, powders, feathers, animals, et cetera, wherever

practical; (3) no desensitization treatment. All previous medication had been of no value.

The allergic patients were tested intradermally, and only the most common allergens were used. These included milk, wheat, eggs, orange, potato, tomato, cocoa, coffee, house dust, pyrethrum, cottonseed, chicken feathers, mixed molds, mixed grasses and ragweed. Thirteen cases showed at least one or more definite positive reactions. All had a previous history of allergic manifestations as well as present symptoms of perennial allergic rhinitis or asthma. This group was composed of naval personnel.

The successful use of this drug in headaches of allergic origin suggests that headaches not responding to D.H.E.45 should be those most amenable to histamine desensitization. This treatment offers another clue in the differential diagnosis of headaches.

#### TYPICAL CASE REPORT

W. C. B., a young man, aged twenty, had chronic bronchitis and a "stuffy" nose for many years, occurring at various times of the day and worse during the night. Two years ago he developed asthma following a spell of virus pneumonia. For one and a half years, he has had headaches about once a week, usually behind the left eye but often bilateral, pulsating in character and frequently associated with nausea. His nose was congested during the headache spells. Dust and smoke caused sneezing spells. There were no known food allergies.

Physical examination was essentially normal except for a marked bilateral allergic edema of the nasal mucosa especially the turbinates. Intradermal tests using fifteen common allergens revealed 4 plus sensitivity to house dust and to chicken feathers.

Elimination diets were of no avail. Various medicines gave no relief. 1 c.c. D.H.E.45 given intramuscularly relieved him in one hour. Formerly these headaches lasted twenty-four to forty-eight hours, requiring bed rest. He was told to return at the onset of a headache for another dose of D.H.E.45. The next attack was relieved in fifteen to twenty minutes and did not recur. He was given five more injections in the next two months for similar headaches, each attack being relieved in fifteen minutes to one hour. There were no side effects or toxic reactions. The headaches have been less frequent and less severe recently. The D.H.E.45 given early in the attack, gave more prompt relief than when injected after the headache had been present for hours. This was also noticeable in other cases.

#### CONCLUSIONS

1. Dihydroergotamine is useful in headaches of allergic origin rather than the idiopathic type.
2. It relieves allergic migraine headaches in one to three hours.
3. The incidence of toxic or side effects is negligible.
4. Although this series of cases is small, dihydroergotamine (D.H.E. 45) promises to be a most useful agent in the symptomatic treatment of migraine and is worthy of further investigation.

*(Bibliography on Page 140)*

## FLEABITE REACTIONS

### Clinical and Experimental Observations and

### Effect of Histamine-Azoprotein Therapy

MILTON M. HARTMAN, M.D., F.A.C.A.  
San Francisco, California

THE damage caused by the flea to the human race has been depicted in its extremes in song and story. The blight of the Black Plague has been the gruesome subject of many medieval and modern medical authors, and the annoyance caused to gentle ladies of the Russian Court has been immortalized in Moussorgsky's "Song of the Flea." But in between these poles of demise and discomfort there is a middle region about which relatively little heretofore has been said or done. The author has reference to a state which has variously been referred to as allergy, hypersensitivity, sensitivity, or idiosyncrasy to fleabites. When the ordinary individual is attacked by a flea, he usually exhibits a few small, red papules, often with tiny hemorrhagic centers, and the itching is bearable and over in a few hours. In a couple of days the lesions are no longer visible.

Flea allergy may take several forms: In the localized papular form the lesions swell tremendously, getting red and hard, and itch maddeningly. The visible and subjective evidence will persist for a week or ten days. Some of these lesions will go on to give a localized bullous or purpuric form. The generalized forms may or may not be accompanied by the abnormal original local lesions mentioned. A generalized pruritis without visible lesions other than the original points of attack occurs. A widespread urticarial reaction is common and in some cases the urticaria assumes a vesicular or bullous form; these lesions may persist for two weeks. Angioneurotic edema removed from an original point of attack is rare. Asthma occurs occasionally in conjunction with the skin reaction but nasal, gastro-enteric, or migrainous symptoms are practically unknown. Needless to say, the itching may beget psychiatric problems, and the inevitable scratching often seems to make the itching worse rather than better. The other sad feature of the scratching is that, especially with children, it leads to secondary infections such as impetigo, lymphangitis, lymphadenitis, furuncles, and carbuncles, all of which can be quite serious.

Local anti-pruritic therapy is only partially successful as can be attested by the imposing list of preparations used, and when the body is completely covered becomes well nigh impossible. Prophylaxis against fleabites consists of either avoidance of exposure to fleas (such as keeping away from animals and crowded places), or treating the body, clothes, or sleeping quarters with insect repellents or insecticides. Most people do not relish the self-imposed isolation, and the repellents have the disadvantage of odor, irritation, allergenicity in themselves, and necessarily continuous

renewal. Furthermore, many insect repellents were more successful in repelling one's friends than the fleas. It was inevitable, then, that if a person wished to lead a normal life he would sustain more or less fleabites. Quite logically, therapy, acquiescing to this fact, took the direction of trying to immunize or desensitize to the ubiquitous flea. Peptones, non-specific vaccines, and boiled milk injections were tried and were useless. Extracts prepared from the flea itself, using many extracting fluids and many extracting processes, ranging from simple maceration to the Krueger low-temperature steel ball mill pulverization, were completely ineffective in treatment. The author has tried therapy with flea extracts prepared by every means described in medical literature up to the end of 1944; it has been ineffective. Some positive skin reactions were obtained to a 1 per cent extract prepared by grinding fleas in a low-temperature steel ball mill (Krueger process) to prevent denaturation and then sterilized by Berkefeld and Seitz filtration. Even in those cases which reacted positively to this extract there was no perceptible effect with treatment.

Two factors have conspired to make assessment of the value of desensitization treatment difficult and perhaps to delude investigators into thinking they have accomplished results when they have not. The first is a natural variability in the frequency of fleabites. For some unaccountable reason there may be long periods of time in which few if any fleas are present and then they can become abnormally numerous. The second factor is a definite tendency to spontaneous auto-desensitization, which may occur just at the time that therapy is in progress. Here on the Pacific Coast it is quite frequently observed that people recently arrived from the Eastern United States are tremendously annoyed by fleas, whereas they were not in their former home. In the course of approximately a year, however, they usually experience no more difficulties from fleabites than the native Westerner. Any cases, therefore, selected for therapy should be from among newcomers during the first few months after their arrival or in residents who have had their symptoms undiminished for at least a year.

#### PRELIMINARY EXPERIMENTS ON NATURE OF FLEABITE REACTIONS

Epinephrine administered subcutaneously within fifteen minutes after the flea bites usually reduces the amount of local reaction and/or aborts generalized reactions. Given after this period the effect of epinephrine is only temporary. In sensitive patients presenting multiple initial lesions one may inject procaine into some of the papules, leaving the others as controls, and note that the anesthetized lesions do not become as large or persistent. In two highly sensitive volunteers who invariably developed generalized urticaria after a fleabite the author could prevent the attack by immediate electrocoagulation of the test site. After eight minutes this procedure was ineffective. An injection of histamine acid phosphate (.7 to 1.5 c.c. of 1:1000) would reproduce the clinical picture in those susceptible to systemic reactions.

The following sequence of events seems probable: The flea antigen (which is probably a digestive enzyme or anticoagulant) unites with the flea antibody of sensitized people. This union takes place on the cell membranes of skin cells with the consequent release of histamine (or similar H-substances). This reaction is usually localized in scope, but enough histamine may be absorbed into the circulation to cause reactions at remote points. The mechanical trauma of scratching releases even more H-substance from already more or less injured cells.

Other possibilities which cannot be refuted in the light of our present knowledge are that fleas inject an H-substance directly into the lesion or a toxin which kills some cells with the liberation of H-substance. The latter would be more likely than the former.

The author reasoned that whatever the mechanism of release of H-substance, its effects could be nullified by either its decomposition or neutralization. The enzyme histaminase was administered in doses of 15 units every four hours. The result was a definite but not marked diminution in the majority of cases tried, but this was abandoned because of the necessity of continuous administration. Efforts to produce neutralizing bodies by the intradermal or subcutaneous administration of histamine gave some promise but had to be abandoned because of the flushing, headache and occasional urticarial reaction or asthma produced. Histamine diffuses rapidly and is quickly detoxified. Whatever beneficial effects were noted continued only as long as treatment was kept up and were not worth the effort and discomfort involved. The author's experiences with histamine-azoprotein are now reported.

#### DEVELOPMENT AND ACTION OF HISTAMINE-AZOPROTEIN

Landsteiner<sup>6</sup> showed that the diazotization of simple chemicals and coupling to proteins resulted in the formation of an antigenic complex whose specificity was determined by the hapten portion. Recently a method has been developed for the heightening and preserving of histamine antigenicity with simultaneous elimination of its usual toxic effects and the antigenicity of the associated protein. The first step was the despeciation of horse serum globulin by partial digestion with Taka-diestase at pH 3.8 followed by neutralization.<sup>1</sup> The resulting globulin produced no reaction in people known to be acutely allergic to horse serum and dander. Histamine was then combined with paranitrobenzoylchloride in chloroform and triethylamine. The resulting paranitrobenzoyl histamine was then reduced with ferrous sulfate and ammonia to yield para-aminobenzoyl histamine, which was then diazotized and coupled with the despeciated globulin. The histamine-azoprotein produced was separated out, purified, and redissolved in weak alkali. This solution is adjusted to a pH of 7.4. A 3 per cent antigen solution contains .8-1.0 mg. of bound histamine per c.c.; there is no free histamine. This antigenic complex stimulates formation of his-

tamine neutralizing antibodies without producing histamine reactions.<sup>5,7</sup> M. Cohen showed that these bodies were specific for the histamine, not the azo or protein portion of the complex, and that in certain patients histamine-azoprotein produced a capacity for very rapid histamine neutralization.<sup>3</sup> He also demonstrated an increased skin threshold to histamine administered by iontophoresis in histamine-azoprotein treated patients<sup>3</sup> and increased refractoriness to eserine stimulation.<sup>4</sup>

Sheldon and his associates treated a miscellaneous group of patients with allergic disorders and found histamine-azoprotein was of considerable value in the skin disorders.<sup>8</sup> M. Cohen felt that histamine-azoprotein was of particular value in the treatment of urticaria and angioneurotic edema.<sup>2</sup> This seemed like a promising method of treating fleabite sensitivity.

#### METHOD OF TREATMENT

The following succession of doses was administered subcutaneously in the region of the deltoid insertion to adults at four- or five-day intervals: 0.02 c.c., 0.05, 0.1, 0.2, 0.3, 0.4, 0.5, 0.65, 0.8 and 1.0 c.c. Children of six or below were stopped at the 0.65 c.c. level. Patients were advised not to change habits or surroundings and not to use insect repellents or local remedies. The only two classifications of patients were residents, fifteen in number, who had lived in San Francisco and had had symptoms over one year, and newcomers, seven in number, who had had their symptoms only two to four months. All complained of inordinate itching, local or generalized, and were subject to being bitten by fleas at intervals of two weeks or less. The sex distribution was equal.

#### RESULTS OF TREATMENT WITH HISTAMINE-AZOPROTEIN

The results of treatment are assembled in the accompanying table. The effects on the original bites or primary lesions and the generalized or secondary reactions (when present) are separately noted. The use of L.P.L. for large primary lesions is a space-saving abbreviation.

#### COMMENT

A definite response was obtained in every one of the twenty-two cases. The start of benefit was noted between the fourth and tenth injection, fifteen out of the twenty-two patients noting it between the sixth and eighth treatment. All ten patients having large primary lesions only had the size and persistence of their lesions markedly minimized. Four patients had large primary lesions and generalized pruritus but without visible secondary lesions; in these the generalized pruritus was abolished, and the primary lesions diminished in size and persistence. In the five cases in which the large primary lesions were accompanied by urticaria (and angioneurotic edema) the secondary lesions were prevented entirely, and the primary lesions minimized. The two patients whose lesions became purpuric no longer developed this feature, and the child whose large initial lesions used to have a bullous surface now had only normal reactions.

# FLEABITE REACTIONS—HARTMAN

## RESULTS OF TREATMENT WITH HISTAMINE-AZOPROTEIN

Age and Sex	Resident or Newcomer	Previous Duration and Type of Symptoms	Changes Accomplished by Histamine-Azoprotein Therapy	Injection at Which Improvement Noted	Post-treatment Period Under Observation
31-F	N	3 mos. LPL persisting 10 days	Smaller lesions lasting only 2 days. Less itching	5th	6 mos.
43-F	R	4½ yrs. LPL persisting 9 days	Fewer lesions lasting only 3 days. Minim. itching.	8th	4 mos.
50-M	R	8 yrs. tremendous local and subcut. swellings at sites of bites. Generalized pruritis.	Much smaller lesions with minor local pruritis only.	10th	*5 mos.
26-F	N	2 mos. LPL and generalized urticaria	No urticaria. Size and persistence of original lesions halved.	6th	8 mos.
17-M	R	14 yrs. LPL persisting 10 days. Generalized pruritis.	Mild local pruritis only. Smaller primary lesions persisting only 4 days.	8th	4 mos.
13-F	N	3 mos. LPL and generalized urticaria for 2 days after bite.	Only ordinary local reactions. No urticaria.	4th	5 mos.
25-F	R	2 yrs. Primary lesions large and purpuric	Ordinary small papular reactions.	7th	6 mos.
6-F	R	5 yrs. LPL persisting 9 days.	Diminished reactions persisting 4 days.	6th	3 mos.
33-M	N	4 mos. LPL with urticaria & angioneurotic edema following bites	Diminished local reactions only.	8th	7 mos.
3-F	N	2 mos. LPL persisting 8 days	Lesions smaller lasting 3 days only.	5th	3 mos.
22-M	R	15 yrs. LPL persisting 10 days.	Minimal lesions for 4 days only.	8th	5 mos.
5-F	R	4 yrs. LPL persisting 8 days with urticaria	Lesions smaller, lasting 3 days. No urticaria.	6th	4 mos.
45-M	N	3 mos. LPL persisting 9 days.	Lesions smaller, lasting 5 days.	9th	5 mos.
5-M	N	4 mos. LPL persisting 7 days.	Lesions smaller, lasting only 3 days.	8th	4 mos.
28-F	R	10 yrs. LPL persisting 8 days. Gener. pruritis.	Lesions smaller, lasting 3 days. Local prur. only.	6th	†6 mos.
22-M	R	7 yrs. LPL for 9 days. Often purpuric	Lesions small, persisting 3 days. None purpuric.	7th	8 mos.
12-M	R	9 yrs. LPL persisting 7 days.	Lesions smaller, lasting 5 days.	7th	6 mos.
15-F	R	3 yrs. LPL persisting 8 days. Blotchy erythematous rash.	Lesions smaller, lasting 8 days. No erythema.	9th	5 mos.
39-F	R	6 yrs. LPL persisting 7 days.	Lesions minimal, lasting 3 days.	8th	4 mos.
10-M	R	1½ yrs. LPL persisting 10 days.	Lesions tiny. Gone in 4 days.	9th	4 mos.
4-M	R	3 yrs. LPL for 8 days with urticaria.	No urticaria. Small lesions with min. itching.	7th	3 mos.
2-M	R	2 yrs. LPL for 9 days with bullous tops	No bullae. Size and duration of lesions halved.	6th	4 mos.

\*Recurrence at that time successfully re-treated.

†Recurrence at that time successfully re-treated.

LPL—Large primary lesions.

In general, the persistence of all primary lesions reduced to four days or less and the size to one-third or less; the itching was diminished not only in persistence but in intensity. Impetiginized lesions due to scratching did not occur after the eighth injection in any case. At about this point there were no complaints about disturbed sleep.

All cases were followed for a period of three to eight months, with only two recurrences, one at five months and one at six months, both successfully re-treated.

## FLEABITE REACTIONS—HARTMAN

### SUMMARY

1. Forms of skin reactions to fleabites are described. The exaggerated primary lesions may be accompanied by generalized skin reactions.
2. Prophylactic therapy heretofore has been unsatisfactory.
3. Experimental evidence is presented that an H-substance produced at the site of the bite is responsible for the exaggerated local and generalized reactions. The mechanical trauma of scratching increases the amount of H-substance produced.
4. Steps in the development and immunologic background of histamine-azoprotein are outlined.
5. Twenty-two patients who suffered from marked persistent local lesions or generalized skin reactions were treated by the subcutaneous injection of histamine-azoprotein.
6. Good results were obtained in every case. Generalized reactions were completely prevented and all primary lesions were diminished in size and persistence to approximately  $\frac{1}{3}$  of the former figures. Purpuric reactions in two cases and bullous reaction in one case were transformed into the normal pattern.
7. There were two recurrences after five months, both successfully re-treated.

\* \* \*

Acknowledgment is made to Parke, Davis & Company for part of the materials used in this investigation.

450 Sutter Street, San Francisco

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# Department of Clinical Pathology and Laboratory Procedures

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## DETERMINATION OF PENICILLIN-SUSCEPTIBLE STRAINS OF BACTERIA

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El Paso, Texas

IN this day of rather widespread chemotherapy in the infective respiratory conditions that accompany asthma or other allergies, it occurs to me that rather careful analysis of the conditions presented by the patient must be made before we can properly evaluate the results of our treatment or can categorize those cases that are likely to respond. Particularly with the widespread popularity of inhalation penicillin therapy, I think it behooves us to attempt to learn more about these cases, that we may be able to judge in which cases the treatment is indicated and what results to expect. There are of course many factors that will have to be recorded to accumulate this type of data. At least one of the important factors to be considered is the susceptibility to penicillin of the bacterial flora of the bronchial tree or upper respiratory passages. This is relatively easy to do by a variety of techniques.

A simple technique giving good results in our own laboratory is as follows: One blood agar plate is inoculated with the sputum or nasal secretion in question. If the sputum is relatively scanty in bacteria it can be inoculated direct, but if this shows a tremendous bacterial population it would be desirable to emulsify a small particle of the sputum in 2 or 3 c.c. of sterile salt solution before plating. Care should be exercised in the plating so that a not too heavy growth is obtained. Colonies should be discreet and fairly numerous but separated from each other for best purposes. At one edge of the plate a small well is cut from the agar with a sterile instrument and two drops of penicillin solution containing 100,000 units per 5 cc. is placed in it. The plate is incubated twenty-four hours and examined. One should note the relative proportion of different types of organisms present as exhibited in the side of the plate distant from the well. The relative susceptibility of these organisms to penicillin can be evaluated from the side of the plate adjacent to the penicillin by the distance from the well that growth occurs. A highly susceptible organism should not grow closer than 2.5 cm. to the well. In this manner bacterial flora can be catalogued into several classes.

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Suggestions or articles intended for this department should be submitted to Dr. L. O. Dutton, 616 Mills Building, El Paso, Texas.

1. Those that are practically 100 per cent susceptible to penicillin.
2. Those that are composed of mixed types of organisms, some being relatively susceptible, others not being susceptible at all. The non-susceptible colonies will of course grow completely up to the well.
3. Those specimens showing 100 per cent resistance to penicillin of all strains will show growth completely covering the inoculated area up to the edge of the well.

It is also suggested that desirable addition to this data would be re-studies of the sputum after penicillin therapy to determine the effects that it has had on the bacterial flora and perhaps restudies at intervals to see how long it requires for a similar flora to redevelop in the bronchial trees.

This whole procedure is a relatively simple bacteriological one and any adequately equipped bacteriological laboratory can carry this out. It is a procedure which will be quite applicable to even the small office laboratory, provided an incubator is available. Culture media may be purchased from some central laboratory or it can be made fairly simply from dehydrated culture stock, provided adequate pressure sterilization is available. An excellent substitute for the usual laboratory or hospital autoclave is the much cheaper pressure cooker that is equipped with a steam gauge.

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## NASAL AND SPUTUM SMEARS

L. O. DUTTON, M.D., F.A.C.A.

El Paso, Texas

IN spite of the widespread information concerning the proper use of nasal and sputum smears in the study of the allergic patient, it is my general impression that in many instances we are failing to utilize this valuable procedure to its fullest advantage. The reason for this failure is perhaps due to two factors. The first of these is technical.

There still seems to be a rather widespread tendency to use Wright or Giemsa stain for this purpose. Due to the rather widely varying hydrogen ion concentrations of these secretions, these delicately balanced Polychrome stains do not offer uniform results. Often with them the eosinophiles are difficult to distinguish because eosinophilic granules are stained a rather dirty brown instead of the clear-cut pink or red that one expects to see. On the other hand, not uncommonly, neutrophilic cells show a rather marked pinking or reddening of the cytoplasm and on superficial examination may be misinterpreted as eosinophiles. To secure the best results with these stains one must have very thin film of

material and the cells must be separated and not embedded in too much mucus.

The use of methylene blue technique, advocated by Hansel, is far superior both in ease of application and clear-cutness of results. We have found the following technique to give us extremely uniform results and to be subject to a minimum of technical variations.

Smears are obtained either by nasal swabbing, blowing the nose into cellophane, or some slick paper, or in the case of post-nasal drippings by expectoration. Suitable portions of these specimens are spread on clean slides in the usual manner and are allowed to dry. Excessive fixation by heat is not desirable.

The slides are flooded with a thin film of eosin solution and immediately after flooding are washed in running tap water. Mild differentiation is carried out by flooding the slide briefly (a matter of ten seconds or so) with an alcohol acetone decolorizing solution. The slide is then briefly passed through the running tap water again and the final step is carried out by flooding the slide with methylene blue solution immediately washing in tap water. The whole procedure can be carried out in a matter of thirty seconds or so.

The formula for these solutions is as follows:

<i>Eosin Solution</i>		
Eosin, yellowish, alcohol and water soluble	0.5 mg.	
Ethyl Alcohol	95%	
<i>Methylene Blue Solution</i>		
Methylene Blue for Bacilli	0.3 gm.	
Ethyl Alcohol 95%	30.0 c.c.	
Water Distilled	100.0 c.c.	
(Dissolve Dye in Alcohol—Add Water)		
<i>Alcohol Acetone Solution</i>		
Alcohol 95% Ethyl	50.0 c.c.	
Acetone CP	50.0 c.c.	

With this technique we uniformly find the eosinophilic granules to be stained an intense pink, while all the other elements in the field are stained a uniform blue. The contrast is quite striking. An additional advantage of this stain is that the eosinophiles embedded in thick mucus, or in thickened portions of the smear, are stained quite as intense as those widely separated and the cells can be identified even through several layers of superimposed material.

The examination of such slides should be made first with the low power objective. The eosinophilic cells in such smears stand out readily and are detectable at this magnification. Many samples will have only scattered patches of eosinophilic cells and if the slide is not surveyed by the low power they are readily missed if the oil immersion is used for the entire examination. We cannot emphasize this too much as I have seen smears many times called negative on oil immersion examination alone, yet with the low power and a complete survey of the slides

eosinophilic areas are readily found. After the low power survey, suitable areas should be examined by the oil immersion lense to detect the type of bacteria present and also to search for eosinophilic granules which are widely disseminated through the mucus at times even though intact eosinophilic cells are not present. These granules are of equal significance to the intact cells.

The second reason for failure to obtain satisfactory information from nasal smears is the attempt to draw conclusions from inadequately obtained material or too few observations. It must be emphasized that these examinations have to be repeated before conclusive evidence can be drawn as to the character of the nasal secretions. Oftentimes the secretions are too watery and devoid of cellular elements to be of any value. And, oftentimes a superimposed infection of temporary nature will obscure the allergic nature of the exudate for a short period. Perhaps one of the most valuable uses of the nasal smears is the following of the progress of many of these cases of combined asthma and hay fever, who show periodic variations from the allergic to infective nature of the nasal reactions. Without periodic observation during these cycles of symptomology, particularly in children, one may be entirely unaware of the mixed and variable nature of the etiology of their symptoms.

I hope I may be pardoned for bringing this subject before you, as none of it of course is original with me. Doing so is prompted by my impression that too many of us are allowing this extremely valuable procedure to fail to give us the information and understanding of our cases which it is capable of giving.

### D.H.E. 45 (DIHYDROERGOTAMINE) IN THE TREATMENT OF ALLERGIC MIGRAINE

(Continued from Page 130)

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The author reports two cases in which cataracts developed during the active stages of eczema and neurodermatitis. Such association presents no more hazards for operation than does cataract complicated by other diseases.

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*Effect of Ephedrine Sulphate on the Red Blood Count of Humans*. Harris, A. M., and Davis, J. E.: *Proc. Soc. Exp. Biol. & Med.*, 54:195, 1943.

Red blood counts, leukocyte counts and hemoglobin determinations were done at frequent intervals before and after the daily administration of 50 mg. ephedrine sulphate to seven normal persons. A mild, but appreciable polycythemia was produced in three weeks; disappearing, however, in some of the subjects in the fourth week. No deleterious effects were produced.



*Photograph by Fabian Bachrach*

HARRY L. ROGERS, M.D.  
Philadelphia, Pennsylvania  
*President, 1945*

# Editorial

*The opinions expressed by the writers of editorials in the ANNALS are individual and do not necessarily represent the group opinion of the Board or of the College.*

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## BLAZING THE TRAIL

Progress in allergy, as in all other specialties in medicine is dependent upon efficient organization and education. The success of organization is dependent upon the wholehearted co-operation of all its members. There must be no dissension within its ranks.

Many major advances in civilization, as well as in medicine, were made in spite of opposition and intolerance. New theories in medicine often become outmoded or disproven. Progress may be impeded, therefore, by those who adhere to their beliefs. Virchow and his associates set back our knowledge of tuberculosis twenty years because of his "dualistic theory" and resentment of Robert Koch. Our knowledge of cancer, syphilis and other diseases were also retarded for the same reason. Only by efficient organization and education can these impediments be eliminated.

Indeed, there is great need for further education and its dissemination in allergy. The problem is almost an unsurmountable one. Methods of diagnosis and treatment must be standardized. In general allergy today, there is too much individualization on the part of the allergist in the management of the patient. It is the chief aim of the College, therefore, to solve many of these problems.

The American College of Allergists was incorporated November, 1942, as a non-profit organization. The aims and purposes of the College as set forth in the charter are:

- (a) The establishment of an organization of qualified medical men and scientists of good standing who shall meet from time to time for the purpose of promoting and advancing the study, research and clinical knowledge of allergy as it applies to the various specialties in medicine;
- (b) To maintain and advance the highest possible standards among those engaged in the practice of allergy;
- (c) To perpetuate the best traditions of medicine and medical ethics;
- (d) To establish standards for the qualification and procedure for the certification of men engaged in the specialty of allergy;
- (e) To maintain the dignity and efficiency of this specialty in its relation to public welfare;
- (f) To promote friendly intercourse among those engaged in the practice of allergy.

Space will only permit referring to some of the things already accomplished as set forth in these clauses:

## EDITORIAL

(a) The College was the first allergy society to elect as associates, immunologists, bacteriologists, pharmacologists, biochemists, plant pathologists, botanists, et cetera, and receive their valuable consultation, services, and advice.

(b) *ANNALS OF ALLERGY* was the first publication devoted to allergy to publish practical clinical papers as well as investigative allergy, to inaugurate an editorial, a questions and answers, a news item, and a comprehensive review of the allergy literature department. The College through the courtesy of Dr. George E. Rockwell has the use of a central laboratory for the investigation of allergens, and under his direction the first work on co-operative research in allergy by members of the College is now being successfully carried out.

Prior to establishment of the College, with the exception of an annual week-end International Forum and a two-day meeting of the Southwest Forum, there was no attempt to hold instructional courses in allergy outside of New York City. The College initiated intensive instructional courses at its first annual meeting in Chicago in 1944. Since that time a Fall course was held at St. Louis, and last November an unusually successful course was conducted for a week at Thorne Hall, Northwestern University, Chicago. The first of the annual regional instructional courses was held last month at the University of Oregon Medical School. Next November there will be an intensive course conducted by the College at the Jefferson Medical School, Philadelphia. The College was the first society to establish research fellowships in allergy. In the three and one-half years of its existence, three such fellowships have been established through loyal friends of the College, one at the Mayo Foundation under the direction of Dr. Charles F. Code, one at the University of Cincinnati under Dr. Matthew Logan, and recently one on Dermatologic Allergy under Drs. Stephan Epstein and Rudolf Baer.

(d) The January-February, 1946, issue of the *ANNALS* contained an announcement of certification in allergy by The American Society of Certified Allergists, division of the College, and reserves the right to properly qualify physicians as specialists in allergy through the American Board for the Certification of Allergists. This move was inevitable in the light of existing conditions and already applications for Certification are being received by the secretary of the new division by the most representative allergists in the United States, many now subcertified in allergy, who believe that allergy should now be recognized as a separate specialty.

The Founders Group of this new Society and the American Board for the Certification of Allergists will be composed of unquestionably qualified leaders in allergy in their respective specialties.

(f) The College is a member of the International Association of Allergists, and the first Pan-American Congress in Allergy will be held under the auspices of the College at San Francisco at its next annual session, June 28-30.

## EDITORIAL

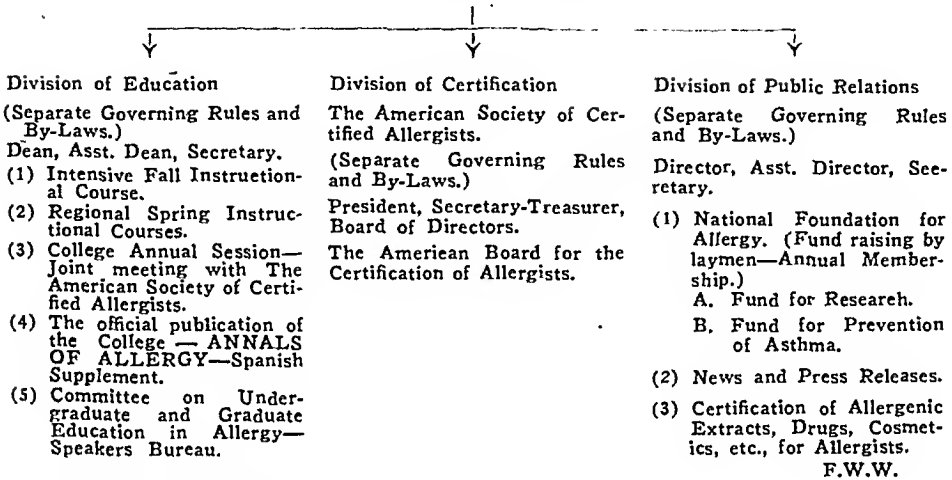
The following outline more clearly defines the functions of the three divisions of the College, which for the greater part are now operating.

We are greatly encouraged to see other allergy groups now adopting many of these plans, since there is so much to be done for allergy that earnest co-operation can never be misconstrued as duplication of effort.

### THE AMERICAN COLLEGE OF ALLERGISTS, INC.

#### Staff of Officers

President, President-Elect, First and Second Vice Presidents,  
Secretary-Treasurer, Board of Regents (10 members)  
(Constitution and By-Laws)



### OUR GUEST SPEAKER

The College will be honored by the presence of the eminent Robert Doerr, M.D., Ph.D., Professor Emeritus of Hygiene and Bacteriology at the University of Basel, Switzerland, at the Second Annual Meeting to be held at the Clift Hotel, San Francisco, June 28, 29 and 30. On his arrival in this country he and a group of his close friends will be entertained in New York at a testimonial dinner by the College.

Doctor Doerr was born on November 1, 1871, in Tésco, Hungary. He studied in Vienna and received his M.D. there in 1897. After graduation he became a medical officer in the Austro-Hungarian army, and while in military service he specialized and qualified in general and experimental pathology, and devoted himself to scientific research in the fields of microbiology and hygiene.

During the course of an epidemic of papataci fever among the troops in Herzegovina the malady received the attention of Austrian military physicians, and in 1908 a commission consisting of Doerr, Franz and Taussig proved it to be a virus infection transmitted by the sand-fly (*Phlebotomus papatassi*). They were the first to prove that infected sandflies could be transported from an endemic area of the disease to a country

where it did not occur and the conditions reproduced in the latter by permitting the insects to bite human volunteers.

During the first World War Doctor Doerr was Director of the Army Bacteriological Laboratory especially concerned with sanitary conditions in the army.

In 1919, at the end of the war, he went to the University of Basel as Professor of Hygiene and Bacteriology where he has remained ever since, refusing many offers of other posts (Robert Koch Institute in Berlin, Universities of Freiburg, Monaco, Marburg).

Doctor Doerr is a member of many scientific societies and the recipient of many honors such as the Aronson prize, the Schneider gold medal from the University of Würzburg, the Marcel-Benoist prize. He is a corresponding member of several scientific societies (Swedish Academy in Lund, Académie de Médecine de Paris, et cetera).

Two Festschriften have been published in his honor; one in honor of his 60th birthday in *Zeitschrift für Hygiene und Infektionskrankheiten*, 1931, and another in honor of his 70th birthday in *Schweizerische medizinische Wochenschrift*, 1941.

His published works are too numerous to list here, although all allergists should read "Allergie und Anaphylaxie" (Handbuch d. path. Mikroorg., 1913) and "Allergische Phänomene" (Handb. d. normalen und pathologische Physiologie, 1929).

Doctor Doerr will present a paper before the College on "Integration and Differentiation of Allergic Phenomena," and is being made an Honorary Member. He will also be introduced at the Pan-American Congress, a section of the International Association of Allergists, at their session under the auspices of the College at the Clift Hotel, Friday afternoon, June 28.

## COLLEGE EX-SERVICE MEMBERS—AN APPRECIATION

One of the greatest manifestations of loyalty to the College has been the unusual promptness of the members when meeting their financial obligations upon their return to civilian practice. This is the kind of stuff upon which the College has been built and which has made it possible to function as it has. The officers of the College owe a debt of gratitude to the members, about 125, who served in the late World War.

During the war there were no annual meetings or any advantages obtained by the members who remained at home. Those at home tried to keep the faith by developing the College, setting up new vital departments and placing the College on a firm financial basis when undertaking new projects, which may be beneficial to all in the College when resuming important postwar activities.

ANNALS OF ALLERGY was mailed regularly to every member in the Service. Changes of address were made with many members at least a half dozen times. It is obvious that many of these went astray, especially

when the publishers did not receive notice of a change of address. The publishers are trying to replace copies for those who have not received them. The College pays the publishers \$6 for every member per year for the annual subscription to the ANNALS. This subscription is included in the annual dues.

We realize that although remittances may not have been a hardship to a number who were high-ranking officers in the Medical Corps, it was, no doubt, to others.

In the near future the College Honor Roll of those who served in the armed forces will be published in the ANNALS.

F.W.W.

## SPINAL ANESTHESIA IN THE THERAPY OF PULMONARY EDEMA; A PRELIMINARY REPORT. Sarnoff, S. J., and Farr, H. W.: *Anesthesiology*, 5:69, (Jan.) 1944.

The authors add spinal anesthesia to the already accepted methods of reducing pulmonary edema: a sitting position by the patient and venesection. Three patients with pulmonary edema were given spinal anesthesia; 50 mg. of procaine hydrochloride per c.c. spinal fluid were administered to patients in a sitting position while leaning forward. These three cases are reported in detail. The mechanism of relief by this method cannot be stated with finality. The etiology of pulmonary edema is that the left ventricle cannot maintain stroke volume equal to that of the right, causing a pressure to be built up in the pulmonary system with extravasation of fluid into the alveoli, diminished vital capacity and hypoxia. Action of the anesthetic may be: (1) a pooling of blood in muscles, spleen, etc., with decreased return to right heart; (2) lowered peripheral resistance as result of paralysis permitting better left ventricular action; (3) diminution of subjective apprehension in these patients.

Good results are obtained without diminished hemoglobin content of the blood, as results from venesection. When the output of the ventricles is nearly equal, edema diminishes in intensity. Improvement in pulmonary edema can be accompanied by decreased cardiac output.

## IMMUNITY TO TETANUS INDUCED BY A THIRD DOSE OF TOXOID THREE YEARS AFTER BASIC IMMUNIZATION; BASED ON A STUDY OF THIRTY-EIGHT ALLERGIC CHILDREN. Peshkin, M. M.: *Am. J. Dis. Child.*, 67:22 (Jan.) 1944.

Thirty-eight allergic children were given a "booster" dose of 0.5 c.c. combined alum-precipitated diphtheria and tetanus toxoid. This was done three years after their basic immunization. A mild reaction was noted in 33 per cent of the children. One systemic reaction occurred in a child given the combined toxoids. An average of two months after the "booster" dose, scratch-test reactions with these toxoids were negative. Adequate tetanus antitoxin titers were noted within one month in all cases. This titer was higher and more prolonged than that following the basic immunization. The author recommends the use of alum-precipitated tetanus toxoid alone for this "booster" dose in order to keep local and systemic allergic reactions at a minimum level.

# Progress in Allergy

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## HAY FEVER

### A Review of the Literature for 1945

GEORGE E. ROCKWELL, M.D., F.A.C.A.

Milford, Ohio

Allergists have long been cognizant of the importance of hay fever—during 1945 it reached national importance when a bill was introduced into the Congress of the United States authorizing an appropriation of \$50,000 for research with respect to the cause and cure of hay fever.\*

This review on hay fever deals chiefly with the progress for the year of 1945. However, occasionally where it seemed advisable we have referred to or included earlier work. In order to clarify the work it has been organized into sections dealing with various phases of the subject. The section on drugs includes only those which are of particular interest in the treatment of hay fever; it does not represent a complete review of drugs of value in allergy.

## POLLINOSIS

### *Distribution, Botany, and Weed Control*

Harsh<sup>30</sup> and collaborators published an extensive survey of pollinosis in San Diego County, California, which should be particularly valuable to allergists in that district. Further, it is a model that could well be followed in making surveys of other territories. The data they present is too massive to summarize in a review so it is suggested that all who are interested in this particular subject read the original article. A pollen review of the grass season in Brazil<sup>27</sup> was also published. In most of the territory they report a well defined grass hay fever season extending from mid-May to mid-June. The principal offenders were *Melinis Minutiflora* (Capin gordura or C. Melando) and *Cynodon dactylon*. A symposium on allergy in the Air Surgeon's Bulletin included a paper dealing with hay fever-exciting plants in the Southwest,<sup>5</sup> also another on the treatment of hay fever and seasonal bronchial asthma.<sup>56</sup> Both of these papers are restricted and hence we have no information as to what they contain other than that indicated by their titles.

Wodehouse's "Hayfever Plants<sup>67</sup>" is an authoritative book dealing with pollens and pollinations and the part they play in hay fever. It contains a description of the plants known to cause hay fever, where they grow, when they flower; and a geographic regional survey with accurate and recent data on areas throughout the United States, Canada and Mexico. It is fully illustrated. Every allergist should have this text.

The rapid progress being made in the field of botany on growth regulating substances is reflected in a paper by Grigsby<sup>28</sup> on the large scale inhibition of pollen production in ragweed by the use of chemical sprays. They report field tests using di-nitro-secondary-butyl-phenol, penta-chlor-phenol and other chemicals but all of these are toxic to cultivated crops. Greenhouse experiments showed that 2-4 D and other similar materials in low concentration stopped the growth of the terminal buds

\*Oct. 3, 1945, Mr. Lane of Mass. introduced H. R. Bill 4279.

of ragweed. The leaves remained green but no pollen was produced over a two-month period. They suggest that such a spray might prevent the production of pollen by common ragweed without having the undesirable feature of complete destruction of vegetation. They plan to try this in extensive field experiments.

To the writer's knowledge no new papers have been published on the much discussed subject of X hay fever. However, Dr. Homer Prince writes to us as follows: "We do see certain cases of hayfever that do not appear to be readily diagnosed. We feel that these cases occur the year round. When they occur in the winter, we attribute them to house dust, respiratory infections, and what-have-you. But when they occur in the summer we do not so readily think of the infections, and since we feel that house dust cases should not have trouble in the summer we presume that additional causes must exist. Apparently in Houston we do not have quite as many of these patients as there are further east. Furthermore, there will be years when we will have more of them. I think it is fairly well concluded that there are no undiscovered pollens causing these symptoms. Molds seem to be about the only thing left that would likely be responsible for the trouble. The various molds that have been cultured will not diagnose all cases, although here and there cases are relieved with various mold extracts. Molds that fall into the basidiomycetes might be particularly responsible. These comprise the rusts and smuts and related forms, and apparently they must be secured from their hosts for extraction which further complicates the problem."

## ATMOSPHERIC STUDIES

Courtright and Courtright<sup>15</sup> presented a well-controlled and extended study on the reactions of 350 guinea pigs which were sensitized and shocked by inhalants of horse dander under various weather conditions. Their results definitely indicated that the weather condition affects the reaction of the animal. This article is well worth reading.

Brown, et al.<sup>9</sup>, in a statistical study, found that there were an increased number of new colds during periods of falling temperature accompanied by heavy rains; also that smokers showed an increased tendency towards colds.

This is a fascinating subject and any allergist who has treated a group of hay fever or asthma patients is well aware of the effect of the weather on the welfare of his patients. Atmospheric studies together with filtration methods certainly should be worthy of extensive study.

## POLLEN THERAPY

*Dosage, Delayed Absorption, Insoluble Antigens, Booster Dose, Immune Studies, Oral Therapy, and Adjuvants*

Acceptance of the treatment of hay fever by inoculation with pollen extract brought new troubles to the physician, for in trying to get the patient to sufficiently high dosage for protection he encountered both local and systemic reactions. The systemic reactions were particularly undesirable and in order to eliminate them the dose was increased less rapidly which necessitated many more injections. Various lines of investigation were pursued in an attempt to obviate these difficulties, and from these experiments several schools of thought developed.

One on low dosage therapy was championed by Hansel. During the past year he published a paper<sup>20</sup> on this therapy in which he described the method of intradermal testing to determine the size of the initial dose together with subsequent intradermal treatment with these minute doses. For these purposes he uses extracts varying from 1:100,000,000 to 1:1,000 concentration. He states that in testing he never uses more than the 1:1,000 dilution except in the very rare case in which he may use the 1:100 dilution. The writer has had no experience with low dosage therapy except in very hyper-sensitive patients in which cases we have been amazed and gratified by the

excellent clinical results although the maximum dose was very low, but never as low as the doses advocated by Hansel. Some allergists complain of poor results when using the low dosage therapy. Perhaps this is due to their method of use. It is the writer's conviction that the greatest value of this therapy is in selected cases as we feel that the maximum tolerated dose for hay fever cases is the one which gives the best results. However, it is possible that there are two mechanisms of protection, namely: one evoked by the low dosage therapy, and the other evoked by high dosage therapy.

Another group advocated reducing the rate of absorption by suspending the antigen in oil. No recent papers have been published on pollen oil mixtures. However, Gay<sup>25</sup> reported on the nonantigenic properties of beeswax and showed that a mixture of beeswax and oil was adaptable for slowing the absorption of injected penicillin. This might be worthy of consideration in the case of pollen extract.

Others made and used the alum precipitate of the pollen antigen. The alum-precipitated pollen antigen seemed to increase sensitivity instead of decreasing it. Nothing has developed on this method recently and we believe its use has been abandoned.

It had previously been found that the hydrochloride of the pollen antigen was relatively insoluble and therefore slowly absorbed. These qualities make it particularly adaptable for immunization in hay fever cases because its use permits a more rapid increase of dosage with a higher top dose; reduces the visits of the patients; gives much better clinical results; and minimizes systemic reactions. Its clinical use is gradually increasing. Its biggest disadvantage is that it is a little more difficult to prepare. However, in the reprints of the lectures of the 1945 American College of Allergists Instructional Course<sup>51</sup> specific directions are given for making and using this pollen antigen hydrochloride. If the allergist is either too busy or does not have the necessary laboratory equipment for its preparation, it is available commercially.\*

A number of decades ago Besredka introduced the sensitized vaccine by treating the bacteria with their immune serum. Later toxin and antitoxin mixtures were developed and now we find Cohen and Friedman<sup>14</sup> reporting on the preparation of a mixture of pollen antigen and its thermostable antibody serum together with its use on three cases. This report is not very impressive because: (1) conclusions have been made on only three treated cases. (2) The maximum dose given one of these cases was only 5,000 units for ragweed and another was 7,500. In the Ohio area this will give little or no protection to a severe ragweed case. Since these patients had no symptoms the inevitable conclusion must be that they were mild cases of hay fever. (3) It is claimed that by the use of this antigen antibody mixture they are able to effect this protection with fewer doses. Based on the size of these doses they can be practically duplicated with pollen antigen hydrochloride.

Following the advent of the booster dose which was particularly emphasized in the production of immunity to tetanus with tetanus toxoid, Loveless introduced its application to the treatment of hay fever.

The principle of the booster dose is based upon the assumption that protection to hay fever is due to the development of an immunity. In order to substantiate this method of treatment it became necessary to prove that this protection is due to the establishment of immunity. In continuing her studies on immunity, Loveless<sup>47</sup> recently described the technique of the conjunctival test as a guide to clinical immunity in hay fever. She concluded that it reveals the threshold of reaction and thus is an important clinical guide to the amount of specific treatment required by the hay fever patient. Those having a threshold of 350 or better are more apt to have excellent clinical results than those having 35 or less. These figures in themselves cause one to ponder. For one thing her experiments showed that 49 per cent of those having a titre of 35 or less showed satisfactory clinical results. Further, in what class are

\*Delapan. Eli Lilly and Company.

those between 35 and 350? Finally, this data was collected on the eastern seaboard. What about the central states of Ohio, Indiana, and Illinois where the pollen exposure is much higher? When one sees the appearance of an eye with a good reaction he has the distinct feeling that he would not wish to have it happen to his own eye.

By means of precipitation tests Johnson et al.<sup>38</sup> have demonstrated the presence of ragweed antigen in the sera of hay fever patients. They proposed to study the correlation among the amount of this circulating antigen, thermo-stable antibody, and reagins; also the relation of these values to the dosage of pollen extract and the pollen count.

Alperstein<sup>2</sup> described an agglutination test wherein pollen-antigen-coated bacteria were used. Cavelti<sup>13</sup> described improvements in the technique of collodion agglutination. However, it is the writer's opinion that neither the collodion nor the bacterial coated agglutination tests are practical at their present development.

About a decade after Noon introduced pollen therapy in 1911, papers began to appear on the desensitization to hay fever by ingestion of the pollen antigen. This interest in oral therapy is manifested because of the many apparent advantages that it offers namely: no injections, minimum reaction, does not require as frequent visits to the doctors office, and most important makes possible the desensitization of certain persons who would otherwise receive no treatment.

Landau and Gay<sup>43</sup> reported moderate to poor results on the use of propeptans in the treatment of ragweed hay fever. In earlier work Iliff and Gay<sup>34</sup> reported that of 82 ragweed patients treated with oral therapy three obtained excellent relief, 10 had good results, and 39 had fair benefit.

Thiberge<sup>62</sup> published an article in which he concluded that oral pollen therapy in the form of enteric coated pills is effective and may be advantageously used as a supplement to parenteral pollen therapy or in patients who cannot avail themselves of parenteral treatment. He again concluded, as he has in the past, that gastric digestion destroys the activity of the ragweed-pollen antigen. However, he has failed to take into consideration experiments previously reported.<sup>52</sup> In this work it was shown that any loss which occurs in acid pepsin digestion of the ragweed antigen is not due to the digestion, but rather to two factors: oxidation of the antigen; and removal by filtration of the insoluble pollen antigen hydrochloride which is formed. This loss can be prevented by excluding oxygen during the process of digestion, or by the addition of dextrose; and by the neutralization of the digestive mixture before filtration.

It has been the writer's experience that oral therapy in the grass type of hay fever is as effective as parenteral therapy.

Urbach<sup>64,65</sup> reported further extensive studies in animals on oral sensitization and oral de-allergization. These studies were carefully executed and the results are impressive. He presented controlled animal experiments which show that sensitization can be brought about orally and that with certain methods de-allergization can be accomplished by the oral administration of propeptans. The conditions of these experiments are so given that they should be capable of repetition, and it would be well for those who disagree with this theory to repeat these experiments.

Adjuvants have been used in the production of immunity and we now find Kulka and Hirsch<sup>40</sup> reporting that rabbits and guinea pigs were more highly sensitized to ragweed extracts when it was given in conjunction with killed tubercle bacilli, paraffin oil, and Aquaphor. Further the antibody level was more sustained. Boyd<sup>7</sup> found that the addition of a good antigen such as killed *Monilia* to a poor antigen such as hemoglobin enhances the antibody response to the latter. The results reported in the above two papers might explain why some observers get better results when using a cold vaccine along with ragweed immunization than they do with ragweed immunization alone.

## PROGRESS IN ALLERGY

Walzer<sup>66</sup> found that ragweed as well as several other antigens could be transported by electrophoresis through three subjects in the same circuit. Any number of sensitized sites reacted to transported antigen when they were covered with negative saline poles.

### COLLATERAL SENSITIZATION

In the past there have been numerous papers on the importance of collateral sensitization in the successful therapy for hay fever. We feel that during recent years this subject has been neglected both in research studies and in its application by the allergists. We mention it here not because there are any new developments to report but with the hope that it will recall to the allergist the importance of this subject.

### HAY FEVER PANEL DISCUSSION

During the past year the International Correspondence Club of Allergy under the direction of Dr. Forman conducted an open discussion on hay fever. A questionnaire was solicited among the members and the replies appeared in the Club Letters. The first question asked was, whether the observer was satisfied to obtain a marked degree of relief for the patient or whether he insisted on having the patient free of symptoms. Very few of the responses indicated any hope of a *permanent cure* for hay fever; certainly examples are rare. Most observers replied that they strived for complete relief of symptoms for the patient, but more than half of them were satisfied with marked relief.

Another question concerned the results actually obtained. Many of the allergists in the ragweed area reported 90 to 100 per cent results after the first season of treatment. Generally these high figures referred to cases of uncomplicated hay fever. More than half considered 75 per cent results to be satisfactory. Constitutional reactions have been minimized by careful observation of the patient's reaction, adjustment of dosage, and cautious technique.

The survey showed the perennial type of treatment was preferred by most observers. However, the type of treatment frequently depended upon the time of the season at which the patient presented himself, and hence pre-seasonal and co-seasonal treatments were used extensively. It was learned that in most instances treatment was not entirely discontinued during the hay fever season: many continued on a greatly reduced dose at longer intervals. No general estimate of the maximum dose used can be made since the replies covered such a wide range.

Another question asked how much emphasis was placed on other factors such as diet, swimming, nursing aids, etc. The replies indicated that almost 90 per cent do place some emphasis on these other factors, particularly on diet. It was learned that an overwhelming percentage do not use respiratory vaccines as part of their routine treatment. When used at all the vaccines were generally stock preparations.

Some critics suspect the allergists of adopting a ritual to impress the patient. This was greatly discredited by those replying to the questionnaire. Most of them claimed to have a standard procedure which was designed to impress the patient with the importance of following instructions minutely, but they all insisted that psychology cannot do much to convince the patient that he does not have hay fever.

### DRUGS

*Hapamine, Vitamin C, Ethylene Disulphonate, Antihistamine, Butanefrine,  
and Nasal Sprays*

Hapamine (Histamine-azoprotein) was introduced to the profession for the development of immunity or desensitization to histamine. In the past several years numerous papers have reported good to indifferent results with Hapamine: during

1945 the International Correspondence Club of Allergy published several letters on this subject.

Edrington<sup>19</sup> and Braden<sup>5</sup> each reported a case of severe systemic shock following a small injection of Hapamine. In each case the patient was cleared of allergic symptoms following the very severe shock. Freund<sup>23</sup> described a reaction to Hapamine in which the patient developed a fever of 103° and showed glandular enlargement. Epstein<sup>20</sup> reported two cases which developed neuritis while receiving Hapamine. He suggested that before administering Hapamine, intradermal tests be done with 0.02 c.c. of a 1/10 dilution of Hapamine, and also scratch tests with Parke Davis purified horse protein. If both of these tests are negative, he feels that it should be safe to use Hapamine. On the other hand Hawkins<sup>33</sup> wrote that she had no less than phenomenal results with very small doses of Hapamine in cases of neuritis and even arthritis. Bowen<sup>6</sup> treated six cases of ragweed pollinosis with Hapamine and reported six failures.

Friedlaender and Feinberg<sup>24</sup> studied Vitamin C in the treatment of a series of hay fever cases. They concluded that hay fever patients had a normal blood level of Vitamin C, and that doses of 500 mgs. daily did not change the course of hay fever or asthma. Brown et al.<sup>9</sup> suggested that Vitamin C possibly acts on the virus of the common cold.

Ethylene disulphonate is still the subject of much controversy. Recent work includes a report by Kurland and Bubert<sup>42</sup>; one by Archibald<sup>3</sup>; a paper presented by Ketcham<sup>39</sup> at the meeting of the Southern Medical Association; and a great deal of discussion in the letters of the International Correspondence Club of Allergy<sup>35</sup>, which also gave a complete bibliography of ethylene disulphonate. It is our impression that allergists are of the general opinion that ethylene disulphonate is of little or no value.

New compounds have been prepared which are claimed to have anti-histamine action. Loew et al.<sup>45,46</sup> described the action of beta dimethylaminoethyl benzhydryl ether hydrochloride (benadryl). Mayer and co-workers<sup>48</sup> have developed several anti-histamine compounds similar in their action; one of them, No. 63, shows promise of therapeutic value. Proceedings of the staff meetings of the Mayo Clinic<sup>50</sup> included a symposium of benadryl and its use in urticaria, bronchial asthma, hay fever, physical allergies, et cetera. It was reported that of fifty-two hay fever cases, 75 per cent were benefited. There were certain side effects of the drug including drowsiness, nervousness, trembling, and inco-ordination. In hay fever 50 mgs. twice daily gave many patients almost complete relief, and in most instances this dose was sufficiently small to avoid side effects. Feinberg and Friedlaender<sup>21</sup> reported favorably on its use in urticaria, serum sickness, rhinitis, and possibly asthma. We have used this drug in several cases of urticaria. It gave relief during continued administration but when discontinued the condition returned. It has also given relief in one out of three cases of asthma in which it was used and it has proved of great benefit in several cases of vasomotor rhinitis. Besides the side effects above noted, two of our patients taking 50 mgs. six times a day developed an acute gastrointestinal upset. This drug may prove to be a very valuable adjunct in the management of hay fever.

Lehmann and Young<sup>44</sup> reported good results on the antihistamine activity of diethylaminoethyldihydroanthracene-carboxylate in animal experiments.

Butaneprine is a drug with an epinephrine-like action but differing in a few important characteristics. It requires about twice the dosage employed with epinephrine. It apparently gives equivalent relief in asthma, and although the allergist may use it more in asthma he may still find it a beneficial drug in the relief of hay fever patients. It lacks the pressor effect of epinephrine hence the vasoconstrictor action makes it available for cardiac asthma and less effective in infected cases. Tremor

## PROGRESS IN ALLERGY

and nervousness occur less frequently. We have found this drug particularly valuable in treating children, and for patients who have become sensitive to adrenalin itself. Papers first appeared on butanefrine in 1917 and have continued regularly throughout the years. For those who are particularly interested in this compound we are including a complete bibliography.<sup>10,11,12,16,26,31,32,37,49,55,57,58,59,60,61</sup>

Much has been written on the use of various nasal sprays. Feinberg and Friedlaender<sup>22</sup>, Kully<sup>41</sup>, and Thomas<sup>63</sup> all issued warnings on the prolonged use of nasal vasoconstrictors, particularly Privine.

Abramson and Demeree<sup>1</sup> described a method for controlling particle size in the use of therapeutic aerosols: many constructive ideas are given. Rothman et al.<sup>54</sup> found group specificity present in a man sensitive to procaine.

### CHEMISTRY

Berresford and Cooke<sup>4</sup> reported their studies on pollen moisture and the hygroscopic nature of pollens. Commercial air-dried pollens were found to have a moisture content from 4.6 to 19.6 per cent. They advise that pollens should be machine dried; sealed in air-tight containers and sent at once to the laboratory. Upon receipt at the laboratory they recommend that the pollens be defatted immediately and stored under vacuum.

Roekwell<sup>53</sup> read a paper before the American Chemical Society which presented further proof of the structure of the active antigens in ragweed pollen. A method was given for separating the various antigens as the hydrochlorides: namely by addition of 7.5 c.c. of concentrated HCl to each 100 c.c. of a 10 per cent extract. One antigen is precipitated within a few hours as the hydrochloride. This antigen contains only one molecule of carbohydrate; the remaining antigens are much smaller in molecular size and each molecule contains several molecules of carbohydrate, hence they are much more soluble and do not immediately precipitate out as the hydrochloride. However, if allowed to stand in the cold in the presence of the hydrochloric acid, the carbohydrate is converted to furfural and methylfurfural until each antigen contains only one molecule of carbohydrate, at which point it precipitates out as the hydrochloride. In this way each fraction can be separated and purified. Analytical data was given to show that all of these antigens are carbohydrate-flavonol-peptide complexes somewhat similar to Warburg's yellow oxidation enzyme. Molecular weights vary from the largest which is 4496.084 to the smallest which is approximately 640. All of these fractions are immunologically and biologically active.

### STANDARDIZATION

Standardization of allergens has been the target for several editorials. In the letters of the International Correspondence Club of Allergy<sup>36</sup> it was stated that standardization was not of particular interest but "clinical dependability and results are important." This reflects absolute confusion, for the purpose of standardization is to strive for consistent clinical dependability and results.

One editorial<sup>18</sup> brought up the question of whether or not there is more than one antigen in an extract; possibly one which functions as a skin reactive factor; and one which is effective in treatment.

The American Academy of Allergy voted that "as a temporary expedient, pollen quantity as described in published papers and presented talks shall be explained in terms of units in which one unit is equivalent to quadruple 0 one (0.00001) mgs. of nitrogen as precipitated by phosphotungstic acid."

A controversial editorial<sup>17</sup> pointed out the futility of such a standardization and suggested that possibly the successful standardization of allergens will have to be both biological and chemical. The chemical standardization should be placed upon a

scientific basis such as molar standardization. Molar standardization has the advantage of being the only method proposed which would furnish information on the relative amounts of various antigens present in one extract.

The Standardization Committee of the American College of Allergists is executing an extensive experimental program on standardization; studying both biological and chemical aspects. The report of their data and conclusions when made available should advance our knowledge on this subject. In previous reports they showed that in both pollen and dust extracts there was a marked similarity between biological activity and molar units; whereas other experimental evidence presented showed that this was not true when based upon total nitrogen and phosphotungstic acid precipitate nitrogen.

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(Continued on Page 157)

# Questions and Answers

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In contact dermatitis of the lips, clinically proved to be caused by lipstick, what is the ingredient most commonly causing this condition?

M.D., Portland, Oregon.

The causes of lipstick sensitivity, in order of frequency, seem to be perfume, indelible dye (tetrabromofluorescein), coloring materials, and the base itself.

There are two methods of determining the specific cause of the dermatitis, namely, patch testing by the usual method and also clinical testing on the lips. It is advisable to patch test the patient first and to test clinically only in those cases where the patient does not react to patch tests or in order to verify negative patch test results.

Unscented lipsticks and lipsticks without indelible dye are readily available. Some manufacturers of hypo-allergenic cosmetics carry special stock products and offer lipstick in additional bases and in several special colors. They also make individual formulas where required.

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## PROGRESS IN ALLERGY

*(Continued from Page 156)*

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# *\* In Memoriam \**

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## MAXIMILIAN ARTHUR RAMIREZ, M.D., F.A.C.A.

The College is deeply shocked at the recent death of one of its Active Fellows, Dr. Maximilian Arthur Ramirez, of New York City, on March 4, 1946, at the age of fifty-four.

Dr. Ramirez received his medical education at the University and Bellevue Hospital Medical College, New York, where he graduated in 1912. He was born in Cuba on May 17, 1891; he was professor of medicine at the New York Polyclinic Medical School and Hospital; specialist certified by the American Board of Internal Medicine; past president of the Medical Society of the County of New York; fellow of the American College of Physicians and the New York Academy of Medicine.

Dr. Ramirez served during World War I, and was attending Chief and Director of the Second Medical Division of the French Hospital, and was made Chevalier of the French Legion of Honor.

He was attending physician, New York City Hospital, Welfare Island, as well as Municipal Sanatorium, Otisville; consulting physician, St. Francis Hospital, Poughkeepsie, St. Agnes Hospital, White Plains, and Downtown Hospital.

The College extends its sincere sympathy to the members of his family. We shall feel his loss keenly.

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## ALLERGY AND TUBERCULOUS TRACHEOBRONCHITIS. Oatway, W. H., Jr., Gale, J. W., and Mowry, W. A., *J. Thoracic Surg.*, 13:1, (Feb.) 1944.

The authors have observed that many patients with tracheobronchial lesions had clinical evidence of an allergic diathesis. One hundred patients were bronchoscoped in an attempt to decide the presence or absence of a tuberculous tracheal or bronchial lesion and its characteristics. A complete examination was done and then allergic studies were carried out. Testing was done by the scratch and the intradermal methods. Tuberculin tests were done with a dilution of O.T. of 0.01 mg. and 1.0 mg. Of the 100 patients, eighty had some evidence of tuberculous tracheobronchitis. Of these, 75 per cent were women. Of the eighty patients, fifty were studied completely from the allergic view. There was a correlation between a personal history of allergy and the presence of tuberculous bronchitis by bronchoscopic examination. All the patients reacted to O.T. but there was no association between such reactions and the allergic history. Patients with tuberculous bronchitis were more allergic to routine allergens (by skin test) than were the patients without tuberculous bronchitis. Attempts to desensitize patients with tuberculous tracheobronchitis using tuberculin, do not seem indicated. Desensitization of these patients to other allergens is indicated and legitimate.

# News Items

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Through Dr. Irving Schiller of Boston \$50 was contributed towards the Research Fund by Mr. George Sibley of the College-Town Sportswear, Boston.

\* \* \*

Jack A. Rudolph, Major, MC, Oliver General Hospital, Augusta, Georgia, has recently been appointed Chief of the Medical Service.

\* \* \*

Dr. Frederick Reiss, 816 Fifth Avenue, New York, has been appointed Attending Dermatologist to the Allergy Clinic of the Manhattan Eye, Ear and Throat Hospital and also Consultant to the Surgeon General of the U. S. Army.

\* \* \*

Dr. Isabel J. Wolfstein, who was formerly located at 760 Bankers Trust Building, Indianapolis, Indiana, is now located at 2412 Euclid Heights Blvd., Cleveland Heights 6, Ohio.

\* \* \*

Dr. Samuel S. Burden, Captain, MC, has been transferred from the A.S.F. Regional Hospital at Camp Crowder, Missouri to the Walter Reed General Hospital, where he is now Chief of the Allergy Clinic.

\* \* \*

As the ANNALS goes to press, we sorrowfully regret to announce the death of Dr. William Duke of Kansas City on April 10. A biographical sketch of Doctor Duke will appear in the next issue.

\* \* \*

Dr. Marion Sulzberger is now Associate Director of the Skin and Cancer Unit of the New York Postgraduate Hospital, Columbia University. Dr. Rudolf Baer is in charge of the Allergy Department under the service of Dr. Fred Wise at this same Unit.

\* \* \*

Dr. Henry I. Shahan, 104 Elm Hill Avenue, Roxbury 21, Massachusetts, formerly Major, M.C., at the Veterans Administration, West Roxbury, Massachusetts, is now out of the service, but has been appointed Consultant Allergist to the Veterans Administration.

\* \* \*

At the Spring Instructional Course held at the University of Oregon Medical School, Portland, March 4 through 6, inclusive, five scholarships for the Course at a reduced rate were granted to residents and interns of the Medical School, who were recommended by Dean David Baird. These scholarships were made possible by the Almay, Inc., Grant for undergraduate education in allergy.

\* \* \*

The Southeastern Allergy Association met in Atlanta, Georgia, March 30 and 31 at the Atlanta-Biltmore Hotel. Dr. Hal McCluney Davison of Atlanta, Georgia, was elected president. Dr. J. Warrick Thomas of Richmond, Virginia, was elected Vice President, and Dr. Katharine Baylis MacInnis of Columbia, South Carolina, was elected Secretary-Treasurer. Dr. Marion Davidson of Birmingham, Alabama, and Dr. David Thomas of Augusta, Georgia, were elected to the Executive Council from the membership at large. There were fifty-two doctors registered for the meeting.

## NEWS ITEMS

We are pleased to announce the return from service of the following members of the College and their present locations: Lt. Comdr. Lewis Brown, 162 Roseville Ave., Newark, N. J.; Captain Lewis J. Dimsdale (MC), 18 Blackstone, Sioux City, Iowa; Captain William S. Eisenstadt (MC), 1743 Medical Arts Building, Minneapolis, Minnesota; Captain Meryl M. Fenton (MC), David Broderick Tower, Detroit, Michigan; Major I. M. Hinnant (MC), 10465 Carnegie Avenue, Cleveland, Ohio; Lt. Colonel Louis E. Lieder (MC), 327 Osborn Building, Cleveland 15, Ohio; Captain Lawrence L. Rackow (MC), S. E. Co. 77th Avenue and Limekiln Pike, Philadelphia 38, Pennsylvania; Lt. Colonel James W. H. Rouse (MC), Nix Professional Building, San Antonio, Texas; Captain Harry Paul Schenck, 1912 Spruce Street, Philadelphia, Pennsylvania; Lt. Harold O. Schneider (MC), Salem Clinic, Salem, Oregon; Captain Berthold M. Stern (MC), 6400 North Park Avenue, Philadelphia 26, Pennsylvania; Lt. Colonel Boen Swinny (MC), Medical Arts Building, San Antonio 5, Texas.

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### SECOND INTER-AMERICAN CONGRESS OF CARDIOLOGY

The Second Inter-American Congress of Cardiology will be held in Mexico City, from the 6th to the 12th of October, 1946. All Cardiological Societies of the Continent will take part in the Congress, and, as guests of honor, eminent European cardiologists have been invited to attend.

Doctor Mario Salazar Mallén is secretary of the organization, and he cordially invites any members of the College who might be interested to attend and take part in this Congress. Those wishing to obtain further information about the Congress or the trip to Mexico should write directly to the offices of the Congress, Calzada De La Piedad No. 300, Mexico, D.F., Mexico.

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### BOUND VOLUMES AVAILABLE

The College has contracted with the Dahl Binding Company, Minneapolis, Minnesota, to bind Volumes 2 and 3 of the ANNALS OF ALLERGY. Volume 2 includes the six issues for the year 1944. Volume 3 is comprised of the six issues for 1945.

For those wishing to obtain complete sets, the price for the two volumes will be \$15.00, including binding, postage and handling. The binding is of special dark green buckram on pressboard. Subscribers who have copies of all their ANNALS in good condition for binding can have them bound for \$1.50 per volume if sent to the Office of the Secretary-Treasurer, so that they may be included in this lot; otherwise, binding of single volumes will be \$3.00 per volume.

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### THE REVOLUTION IN RESPIRATORY PHYSIOLOGY

Anoxia has been proven to be a depressant, not a stimulant, to the C.N.S. The same is true of its effect on the respiratory center and even the respiration is stimulated by reflexes in carotid and aortic bodies. Hence breathing is likely to cease when severe anoxemia is removed. Gas tensions and acidity of arterial blood are now thought to be results rather than causes of pulmonary ventilation. The balance between nervous and chemical factors in respiration is disturbed by narcotic drugs. The single effect of all narcotics is to decrease sensitivity of respiratory center to increased CO<sub>2</sub> tension in the blood. Narcotics also tend to shift the balance of respiration to the carotid and aortic body reflexes control. Then the dominant factor in respiratory control is reflex aroused by anoxemia. The respiratory center may cease functioning when these reflexes are abolished by CO<sub>2</sub> administration. The author advises other means of stimulating the respiratory center.—C. F. SCHMIDT, *Anesthesiology* 5:77 (Jan.) 1944.

# BOOK REVIEWS

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**SKIN DISEASES IN CHILDREN.** By George M. Mackee, M.D., and Anthony C. Cipollaro, M.D. Second Edition Revised and Enlarged. 448 pages. 225 illustrations. Price \$7.50. New York: Paul B. Hoeber, Inc., Medical Book Department of Harper and Brothers.

This book is a clear, concise up-to-the-minute presentation of the diagnosis and therapy in the very important field of pediatric dermatology by two widely experienced clinicians and teachers.

There are twenty-one chapters covering the diagnosis and modern therapeutic material of all of the cutaneous affections of infancy and childhood. The fungus disease and diseases due to animal parasites are given in detail.

Of particular interest to allergists is the excellent chapters on Allergic Dermatoses in Children (by Frances Pascher, M.D.); the Eczema Group, The Erythema Group and Dermatitis Medicamentosa or Drug Eruption. The latter half of the text presents Benign and Malignant New Growths, Congenital Cutaneous Anomalies (by Eugene F. Traub, M.D.); The Scaling Dermatoses and the Lichens; Pigmentary Affections; Diseases of the Sweat and Sebaceous Glands, Hair and Nails; the Vesicular and Bullous Diseases; the Contagious Diseases and the Tuberculosis and Syphilis Group of Skin Diseases. The last chapter on Syphilis is written by Herman Beerman, M.D.

Under treatment practical and used prescriptions are given throughout the book along with specific therapeutic measures. The book is very well bound, the print is large and the illustrations are superb when bringing out the details so necessary when illustrating skin diseases.

The use of this book should not be limited to pediatricians, and all physicians particularly the allergists should avail themselves of this important new text.

—F.W.W.

**THE 1945 YEAR BOOK OF DERMATOLOGY AND SYPHILOLOGY.** By Marion B. Sulzberger, M.D., and Rudolf L. Baer, M.D. 559 pages. 72 illustrations. Price \$3.00. Chicago: The Year Book Publishers, 1945.

Although published annually, it is astonishing the amount of new material which appears each year indicating the great advances of our knowledge of Dermatology and Syphilology. With the availability of penicillin its increased combined use with the old antisyphilitic agents is giving promising results.

Detailed observations of studies made on the use of DDT in cutaneous infestations, on the role of fatty-acid powders in the prevention and treatment of certain fungous infections and on chick embryo culture of the micro-organism causing granuloma inguinale are presented.

The continuation of fundamental studies concerning the skin and carcinogenesis, vascular reactions and the psyche and emotions are also reported. The authors stress the importance of the skin in human physiology and morbidity and its value as an organ for scientific research.

The first half of the book is devoted to the leading article dealing with drug eruptions including a detailed discussion of the Atabrin eruption observed during World War II; treatment and preventive measures of common dermatologic diseases; physical therapy; eczema, urticaria and allergy; drug eruptions; hematogenous

## BOOK REVIEWS

dermatoses; other dermatoses; tumors; fungous and other infections; infestations; and venereal diseases.

The remainder of the book presents nearly a hundred pages on investigative studies in skin and venereal diseases. There is a very complete index, the paper of improved quality and the illustrations are good.

The authors have succeeded in awakening new interests in this rapidly expanding field which deserves greater support in the universities, hospitals and the field of research. To be up to date with our knowledge of dermatology and syphilology, every physician should have this new 1945 edition.

—F.W.W.

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the average woman would be lost without certain cosmetic aids to good grooming.

Certain cosmetic ingredients, notably orris root and rice starch, are more highly allergenic than others. It is a good practice for a cosmetic manufacturer not to use such ingredients because there is a relatively high incidence of hypersensitivity to them. Other ingredients, however, which seldom figure as allergens or irritants may nevertheless prove to be the allergic factor.

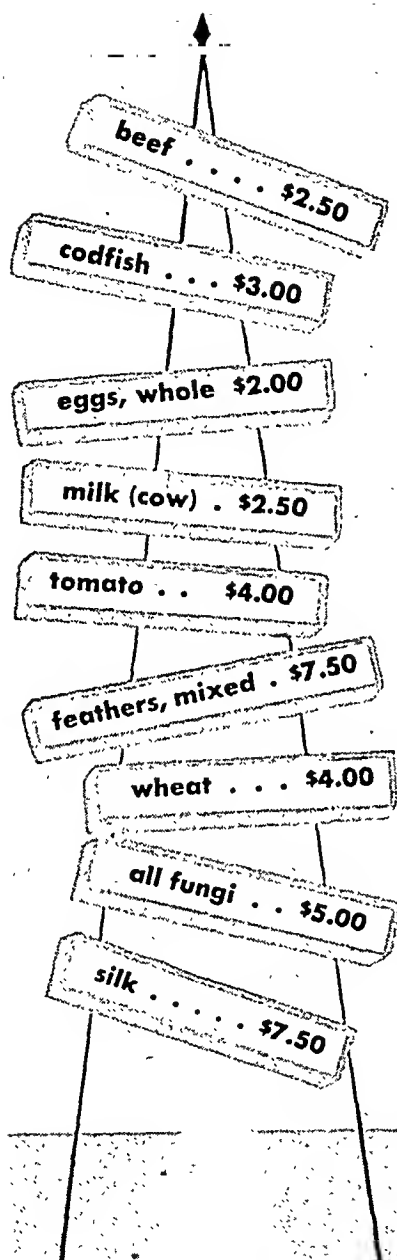
That is why we believe that when there is a history or suspicion of allergy, the subject should be tested with the cosmetic preparations she is using or contemplates using. If tests with the finished products are positive, further testing with their constituents is indicated to endeavor to determine the offending agents. These found, it is frequently possible for us to modify our formulas to exclude them.

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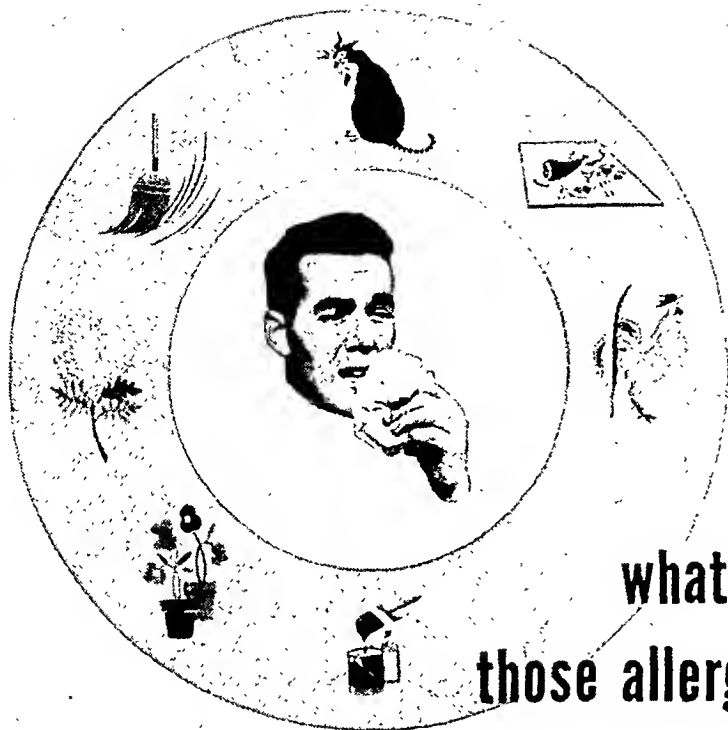
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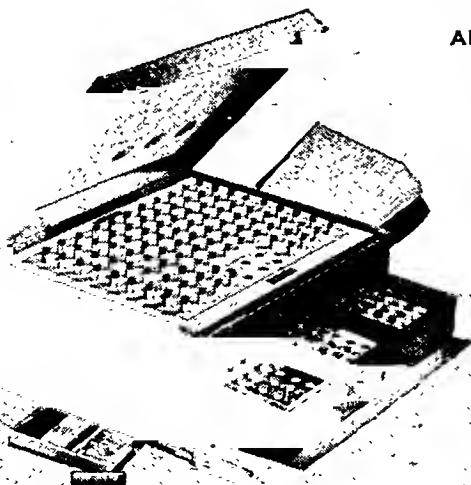
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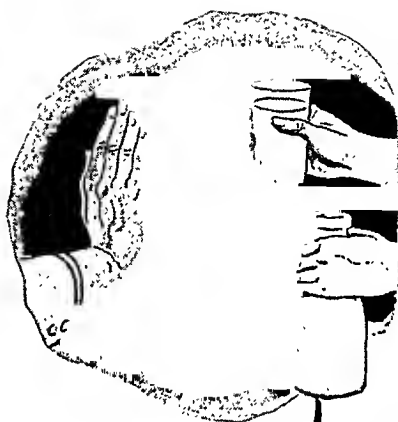


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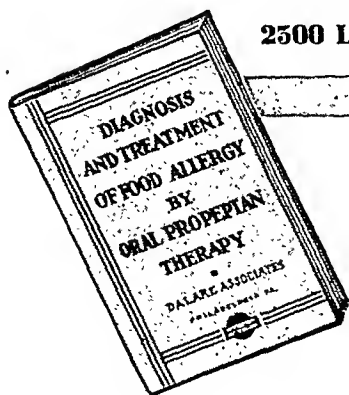
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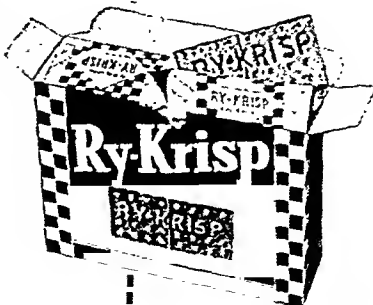
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## *Contents for May-June, 1946*

### BLOOD STUDIES IN ALLERGY.

- V. Variations of Total Leukocytes Following Test Feeding of Foods; An Appraisal of the Individual Food Test.  
*Theron G. Randolph, M.D., F.A.C.A., Chicago, Illinois, and Frank F. A. Rawling, M.D., Toledo, Ohio.*..... 163

### ETHYLENE DISULPHONATE IN CHRONIC ASTHMA.

- H. H. Brenner, M.D., and A. V. Stoesser, M.D., Ph.D., F.A.C.A., Minneapolis, Minnesota* ..... 179

### PENICILLIN DERMATITIS BASED ON TUBERCULIN-TYPE SENSITIVITY.

- Stephan Epstein, MD., F.A.C.A., Marshfield, Wisconsin, and Hermann Pinkus, M.D., Monroe, Michigan.*..... 186

### REACTIONS TO PENICILLIN.

- George W. Truitt, M.D., F.A.C.A., Chadds Ford, Pennsylvania.*..... 196

### COMBINED PENICILLIN AND HYDROGEN PEROXIDE AEROSOL THERAPY IN LUNG INFECTIONS.

- Harold A. Abramson, M.D., F.A.C.A., New York City.*..... 199

### HYDATID ALLERGY.

- Alfonso Graña, M.D., F.A.C.A., Montevideo, Uruguay.*..... 207

### ASTHMA DUE TO BEE SCENT.

- Heber C. Jamieson, M.D., Edmonton, Alta., Canada.*..... 213

### HEADACHES.

- William R. Crowe, M.D., F.A.C.A., Atlanta, Georgia.*..... 216

### DEPARTMENT OF CLINICAL PATHOLOGY AND LABORATORY PROCEDURES:

- Sedimentation Rate—A Diagnostic Aid in Allergy.  
*D. J. Parsons, M.D., F.A.C.A., Springfield, Ohio.*..... 220

### EDITORIAL:

- Bacterial Allergy ..... 223

### PROGRESS IN ALLERGY:

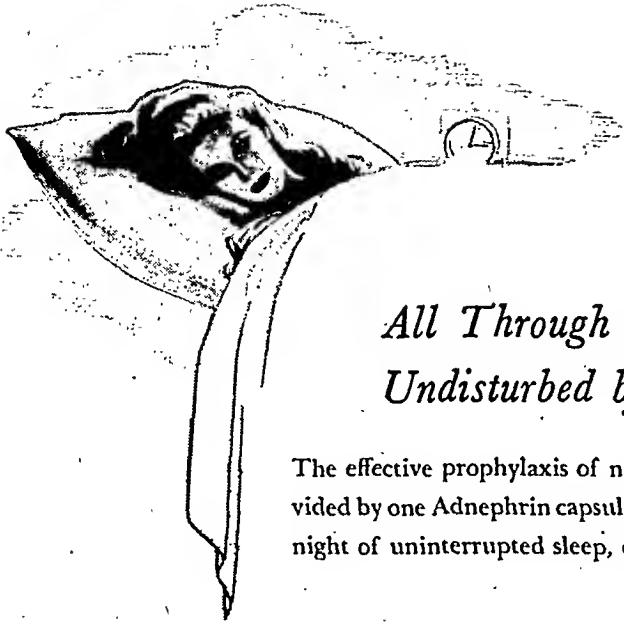
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*Ethan Allan Brown, M.D., F.A.C.A., L. Robert Weiss, M.D., F.A.C.A., and Milton Bilder, M.D., Boston, Massachusetts.*..... 226

### IN MEMORIAM ..... 241

### NEWS ITEMS ..... 243

### BOOK REVIEWS ..... 245

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## BLOOD STUDIES IN ALLERGY\*

### V. Variations of Total Leukocytes Following Test Feeding of Foods; An Appraisal of the Individual Food Test

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ALTHOUGH Vaughan<sup>13</sup> suggested the leukopenic index as a diagnostic aid in food allergy in April, 1934, Rinkel had reported the results of clinical observations following the trial feeding of foods the preceding November (1933). Rinkel<sup>10</sup> subsequently included pre-ingestion and post-ingestion total leukocyte determinations as a part of his technique but continued to stress the diagnostic significance of clinical reactions developed during and following experimental feeding. As the result of more than a decade of observations of food sensitive patients in varying phases of clinical tolerance and intolerance in respect to the specific food tested; Rinkel<sup>11</sup> recently reported a further improvement in the method. This consists of the preliminary preparation of the patient by the complete avoidance of the food in question for four days prior to testing, and the feeding of a second dose an hour after the first if clinical symptoms are not produced during the first hour.

Squier and Madison<sup>14</sup>, employing a diluting fluid of eosin and acetone in distilled water which permits the enumeration of eosin-staining cells in the counting chamber, reported an increase of the cells taking the eosin stain in addition to a leukopenia following the test feeding of an allergenic food. Their method has not come into general use, presumably, because it does not permit a quantitative enumeration of either the true eosinophils or the total leukocytes, due to the rapid fading of all cells in the presence of a hypotonic diluent. However, if serial determinations are made at a

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constant interval from the time of diluting the blood sample, the fading of cells appears to occur at a constant rate following the ingestion of a compatible food. A more rapid "disappearance" of white blood cells following the ingestion of an allergenic food suggests an increased fragility of these cells in addition to the actual leukopenia described by others. For these reasons the ingestion test as employed by Squier does not reveal the same information as does Rinkel's technique or the method originally described by Vaughan. However, in expert hands Squier's and Madison's method is a valuable adjunct in the recognition of specific food reactions. The technical aspects of this procedure have been discussed in greater detail elsewhere.<sup>5</sup>

After the development of a white blood cell-diluting fluid of equal parts propylene glycol and water containing phloxine and methylene blue<sup>4,8</sup>, it seemed desirable to study the hematological aspects of the food and drug response since this method permits an accurate enumeration of eosinophils in the counting chamber in the same sample of blood employed in counting the total leukocytes. The hematologic changes following the trial ingestion of sulfonamide drugs in cases of known sensitivity, and the variation of eosinophils associated with test feeding of allergenic foods, have been described.<sup>5,7</sup> Although a delayed eosinophilia was observed in both instances, this response was inconstant in food allergy; its delayed occurrence does not favor eosinophil measurements as a possible diagnostic method useful in detecting specific sensitivity.

In starting the present study of the total leukocyte response following the trial ingestion of foods, individuals of known sensitivity were first fed the specific allergen in the fasting condition without reference to its inclusion or omission in the preceding diet. Under these circumstances we often obtained hematologic responses which, according to the early reports of Vaughan and others, were at variance with the clinical histories. We then learned that we were testing patients in various phases of specific allergic tolerance, for, as a rule, the cases of known sensitivity had been avoiding the suspected food either partially or completely for some time prior to the test. For instance, we observed several cases of unquestioned clinical sensitivity where the specific agent had been avoided for several weeks or months, in whom trial ingestion of a single dose was not followed by a leukopenia or the production of symptoms. Other instances in which the food in question had been eaten daily prior to the test did not respond with as concise a clinical or hematologic reaction as when re-tested after four days of specific avoidance. In still other instances we apparently missed an early leukopenia in spite of precipitating acute allergic symptoms by performing the postprandial blood counts at intervals of every thirty minutes.

In late 1943 we adopted a technique patterned after Rinkel's<sup>11</sup> individual food test. Only cases of uncontrolled clinical allergy with unknown food sensitivities were used. The food to be tested had been included in the

diet until four days prior to the test, then it was completely avoided for four days and tested on the fifth. All food, medications and tobacco were omitted for at least five hours prior to the test. After resting in the sitting position for thirty minutes, two total leukocyte counts were made to establish a base line. An average to a large serving of the food to be tested was eaten within a period of five minutes and total leukocyte determinations were made at intervals of twenty, forty and sixty minutes after completion of the test meal. If symptoms had not been produced within the first hour after test feeding, a second serving was fed and the patient was kept under clinical observation for an additional thirty minutes.

The total leukocytes of eight squares or the four corners of each side of the counting chamber were counted. Each serial observation was made by the same technician employing the same pipette and counting chamber. The average of two pre-ingestion total leukocyte counts was taken as the fasting level, and only in this respect did the mechanics of the technique differ from that recently advocated by Rinkel.<sup>11</sup> In the graphic representation of results we have found it advantageous to plot the postingestion variation in total leukocytes in terms of percentage rather than numerical deviation from the pre-ingestion level. As a time-saving measure in the calculation of the percentage variation, the increment or decrement percentage may be read directly from a chart.<sup>6</sup> All patients were kept under close clinical observation throughout the test. Pulse and blood pressure determinations as outlined by Rinkel were not performed routinely.

Since applying this procedure as a diagnostic measure in cases of unknown food sensitivity there has been a high degree of correlation between the findings of a postprandial leukocytosis and the current evidence of specific clinical tolerance on the one hand, and a postingestion leukopenia with evidence of clinical intolerance following test or cumulative feeding on the other hand.

#### THE INTERPRETATION OF INDIVIDUAL FOOD TESTS

Vaughan originally suggested that the diminution of 1,000 cells from the fasting level occurring after the ingestion of a food indicated an incompatible blood response. Under certain circumstances, Rinkel and Gay<sup>12</sup> found a decrease of 500 cells to occur in association with clinical evidence of intolerance. From an analysis of cases of proved clinical sensitivity, our experience indicates that a postingestion leukopenia of greater numerical magnitude may be expected in cases having a high basal total leukocyte count, and, conversely, lesser degrees of leukopenia as measured in absolute values occur in cases having a relatively low initial white blood cell level. Particularly in the latter group, acute allergic manifestations may develop after the trial feeding of a food accompanied by a decrease of the total leukocyte count between 500 and 1,000 cells. For these reasons we have found it more satisfactory to express the leukopenia or the leukocy-

tosis in terms of the percentage deviation from the fasting level rather than to employ the numerical expression originated by Vaughan and continued by Rinkel. This method of graphic representation has the further

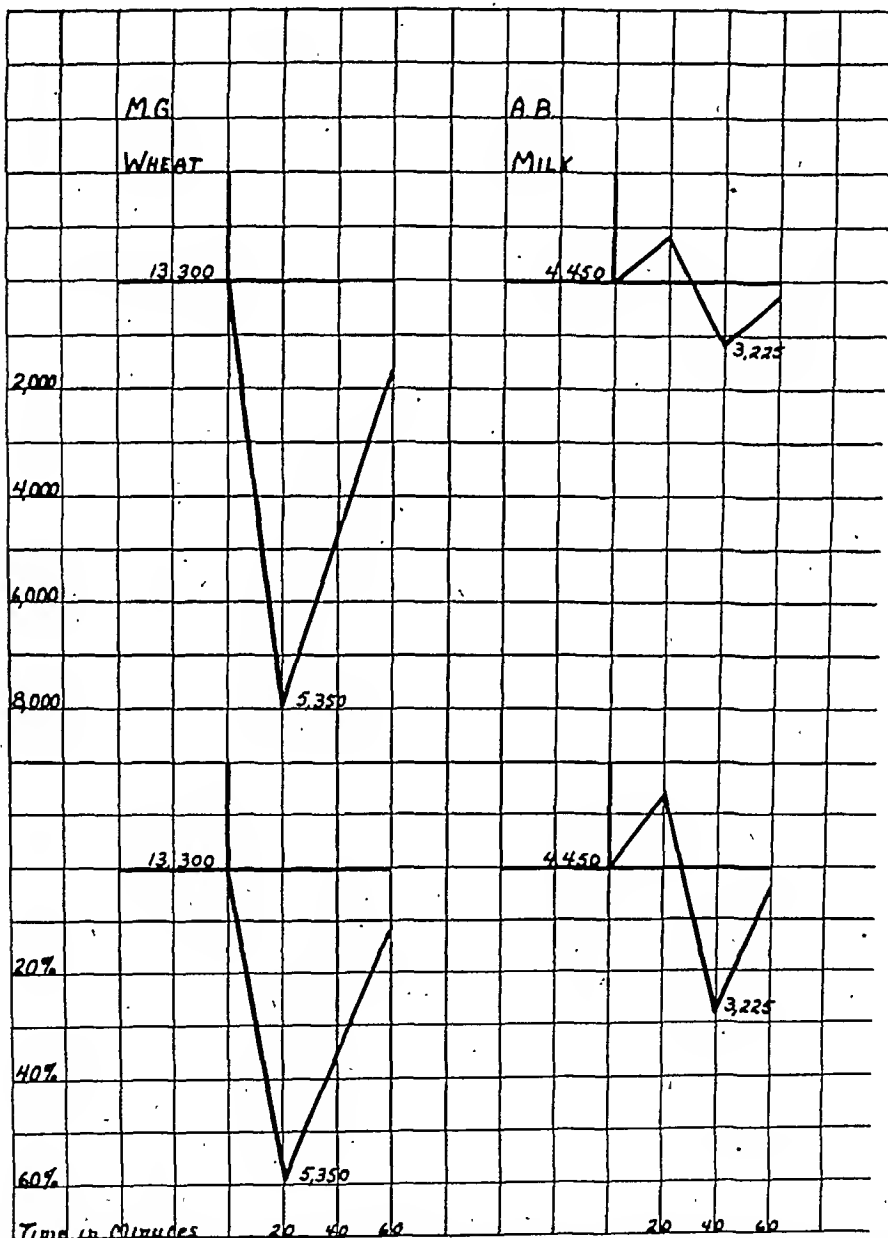


Fig. 1. Methods of plotting the results of individual food tests. Post-ingestive total leukocyte counts plotted according to the numerical deviation from the pre-ingestion level (above), and according to the percentage deviation (below).

advantage that it minimizes the variations occurring from high basal counts and magnifies those arising from an initial low total leukocyte level. These points are illustrated in Figure 1, which shows the test data of

two cases plotted by each method. Although in the first case there was a profound leukopenia, a single feeding failed to produce immediate or delayed symptoms, in contrast to the acute clinical reaction occurring in the second instance in the presence of a minimal blood change.

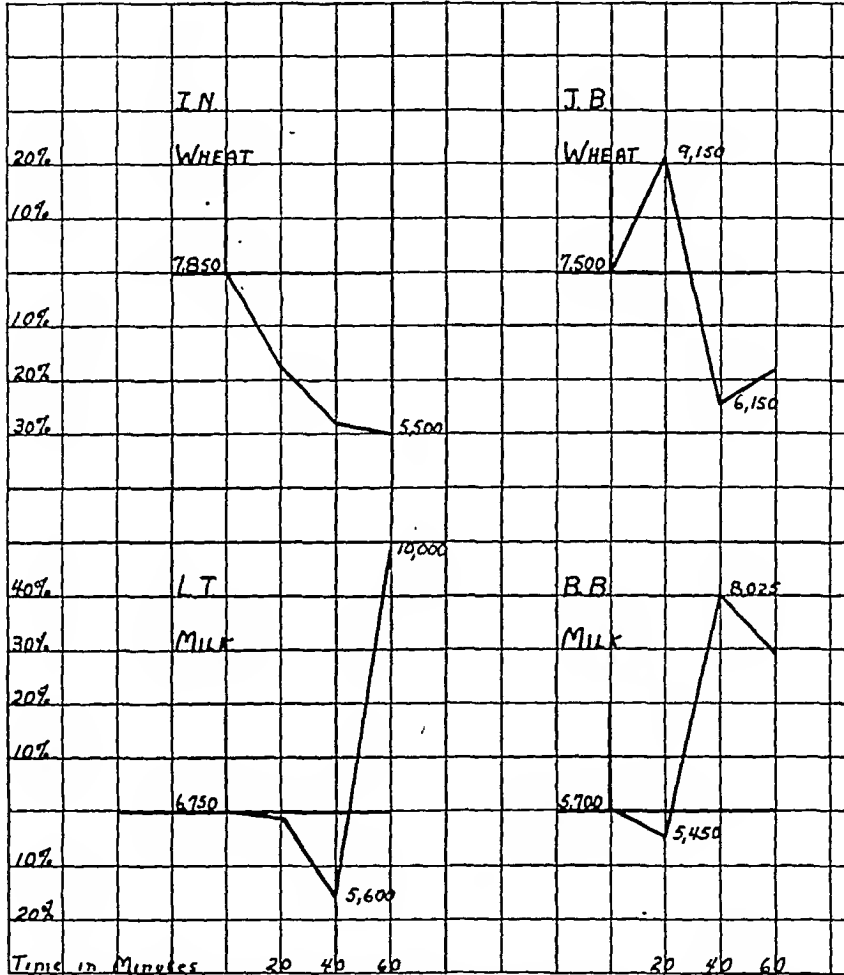


Fig. 2. Instances of positive individual food tests associated with sharp clinical reactions showing abrupt changes in the post-ingestive total leukocyte counts.

We wish to emphasize the importance of the graphic representation of test data; it should always be done before attempting to interpret the results of a given test. One learns by experience to recognize certain patterns of plotted results which are commonly associated with severe reactions. This was pointed out by Rinkel, as well as the fact that sudden changes in the leukocyte level are commonly associated with more severe reactions. Instances of this type are illustrated in Figure 2. Graph 1 of this figure is that of a patient with perennial allergic rhinitis and bronchial asthma who developed mucus in her throat five minutes after the ingestion

of wheat, followed by complete nasal obstruction beginning at ten minutes. Graph 2 is from a patient with perennial allergic rhinitis, gastro-intestinal allergy and allergic headache, who developed a severe headache with dizziness thirty minutes after feeding with wheat. Graph 3 is from a case of

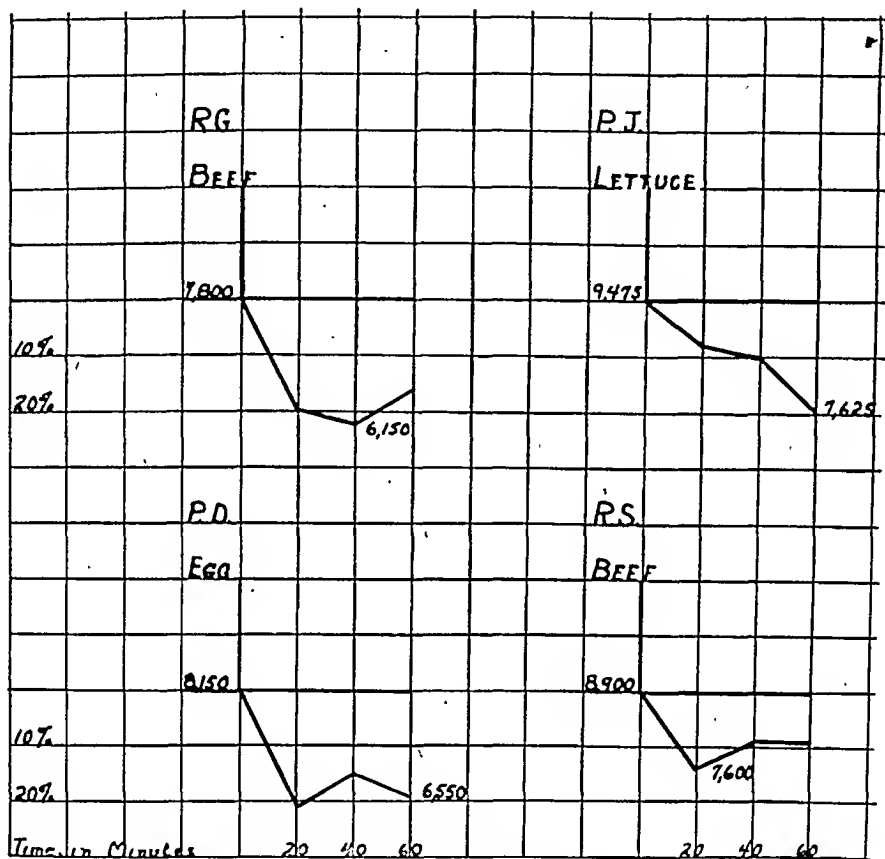


Fig. 3. Instances of positive individual food tests associated with clinical reactions illustrative of commonly encountered blood responses.

allergic headache in whom the trial feeding of milk precipitated sharp head pain beginning two hours after ingestion. In the final graph a significant leukopenia was not measured, although this patient developed severe abdominal cramps three minutes after drinking milk, with excessive belching and nasal stuffiness at five minutes. She had an extreme degree of sensitivity to milk and complete avoidance has been necessary for relief of her perennial allergic rhinitis, bronchial asthma and gastro-intestinal symptoms. It is quite possible that a more significant leukopenia occurred in this instance prior to the twenty-minute blood observation. Obviously, in the event of such a clinical reaction one does not need to rely upon the blood findings to diagnose specific sensitivity. This type of blood response is of rare occurrence.

More commonly observed patterns of reaction associated with allergic

# BLOOD STUDIES—RANDOLPH AND RAWLING

intolerance are listed in Figure 3. Graph 1 is from a patient subject to gastro-intestinal allergy and recurrent urticaria, who developed chilliness and lower abdominal pains forty minutes after the ingestion of beef. Spe-

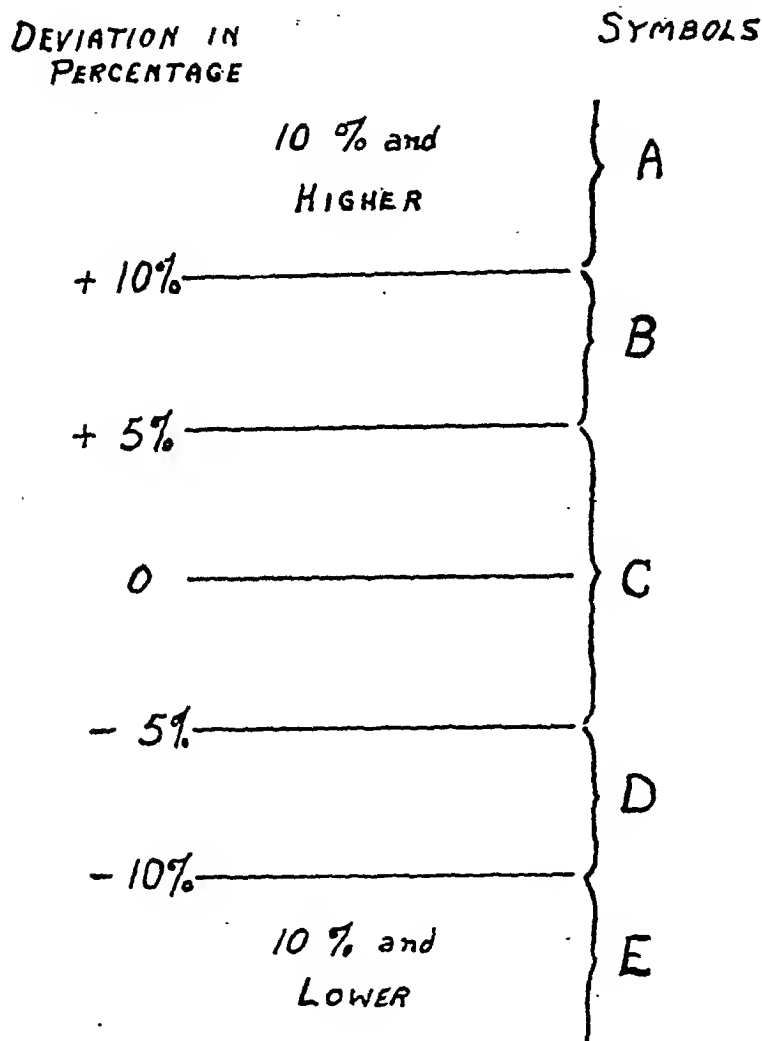


Fig. 4. A scheme for recording the results of individual food tests in terms of symbols representing the percentage variation of post-ingestive total leukocyte counts from the pre-ingestion level.

cific sensitivity was confirmed by continuing its use in the diet with the precipitation of acute abdominal cramps and diarrhea. Graph 2 is from a case of gastro-intestinal allergy with pronounced allergic fatigue, who developed chills at thirty minutes and a headache at fifty minutes following the ingestion of lettuce. Headache with residual fatigue persisted the following morning in association with several liquid stools. The third graph is from a child with infantile eczema, who developed an acute flare of dermatitis between eight and ten hours after test feeding with eggs.

## BLOOD STUDIES—RANDOLPH AND RAWLING

The last graph is from a student with a diagnosis of giant urticaria, who developed an acute attack of hives four hours after the test. Diet trial has proved the specific diagnosis in each of these illustrative cases.

SYMPTOMS					SYMPTOMS					SYMPTOMS					SYMPTOMS					SYMPTOMS					TOTALS	
- +					- +					- +					- +					- +					- +	
A	A	A	36		A	B	A	4		A	C	A	4		A	D	A	1		A	E	A		1	45	1
B	A	A	8		B	B	A	4		B	C	A			B	D	A			B	E	A			12	
C	A	A	9	1	C	B	A	4		C	C	A	5		C	D	A			C	E	A		1	18	2
D	A	A	2		D	B	A			D	C	A	1		D	D	A			D	E	A			3	
E	A	A		1	E	B	A		1	E	C	A	1	3	E	D	A			E	E	A			1	5
A	A	B	4		A	B	B	1		A	C	B	1		A	D	B			A	E	B			6	
B	A	B	2		B	B	B	2		B	C	B	1		B	D	B			B	E	B			5	
C	A	B			C	B	B	2		C	C	B	7		C	D	B	1	1	C	E	B			10	1
D	A	B			D	B	B			D	C	B			D	D	B			D	E	B				
E	A	B			E	B	B			E	C	B		1	E	D	B			E	E	B				1
A	A	C			A	B	C	1		A	C	C			A	D	C			A	E	C	1	1	2	1
B	A	C	1		B	B	C	1	1	B	C	C	2		B	D	C			B	E	C			4	1
C	A	C	2		C	B	C		1	C	C	C	28	2	C	D	C	1	4	C	E	C	2	3	33	10
D	A	C			D	B	C	2		D	C	C	4		D	D	C	2	1	D	E	C		3	8	4
E	A	C	1	2	E	B	C			E	C	C	1	2	E	D	C	1	3	E	E	C	2	3	5	10
A	A	D		1	A	B	D	1		A	C	D			A	D	D			A	E	D			1	1
B	A	D			B	B	D			B	C	D		1	B	D	D	1		B	E	D			1	1
C	A	D	1		C	B	D	2		C	C	D	2	1	C	D	D	3	1	C	E	D	3	3	11	5
D	A	D			D	B	D			D	C	D		1	D	D	D	2		D	E	D		1	2	2
E	A	D			E	B	D			E	C	D			E	D	D	1	1	E	E	D	4	4	5	5
A	A	E			A	B	E	1		A	C	E	1		A	D	E			A	E	E		1	2	1
B	A	E			B	B	E			B	C	E		1	B	D	E			B	E	E	2		2	1
C	A	E		1	C	B	E			C	C	E			C	D	E		3	C	E	E	5	6	5	10
D	A	E			D	B	E			D	C	E	1		D	D	E			D	E	E	6	3	7	3
E	A	E			E	B	E			E	C	E	2	1	E	D	E	2		E	E	E	17	23	23	24
TOTALS			66	6				25	3				61	13				15	14				44	53	211	89

Fig. 5. The results of 300 consecutive individual food tests recorded in terms of symbols representing the percentage deviation of post-ingestive total leukocyte counts from the fasting levels and the presence or absence of associated symptoms.

A series of 300 consecutive individual food tests performed by three different technicians was subjected to a detailed analysis. As a matter of convenience in recording the results, each of the three post-ingestion leukocyte counts was classified as *A*, *B*, *C*, *D*, or *E*, according to the percentage deviation from the average of the two pre-ingestion total white cell counts. The symbols *A* and *E* indicate, respectively, an increase and decrease of 10 per cent or greater, *B* and *D*, an increase and decrease, respectively, of 5 per cent to 10 per cent, and *C*, an increase or decrease within 5 per cent of the basal leukocyte level. The basis of this classification is illustrated in Figure 4. It is apparent that the blood response of a given test may be represented as *AAA*, *EEE*, *BEC*, or any other combination of

# BLOOD STUDIES—RANDOLPH AND RAWLING

the five letters. For instance, Graph 1 of Figure 2 would be designated as *EEE*, Graph 2 as *AEE*, Graph 3 as *CEA* and Graph 4 as *CAA*.

Figure 5 records the blood response of the 300 food tests classified according to these symbols and the presence or absence of symptoms occurring during or immediately following the procedure. Although all possible combinations of the five letters are listed, many combinations are not encountered and certain others are found with relative frequency. One should note the absence of symptoms associated with the *AAA* and related curves containing only the letters *A* and *B*, and the frequency of symptoms in the *EEE* and other combinations containing one or more *E*s.

The statistical significance of these data is more apparent when they are arranged in four-fold tables correlated by the chi-square technique. For instance, in comparing the curves where each post-ingestion count was 10 per cent or greater than the base line average (*AAA*) with those where each observation was 10 per cent or less (*EEE*) in respect to the presence or absence of symptoms, one obtains a chi-square of 16.08.

	Without Symptoms	With Symptoms	
<i>AAA</i> .....	36	0	36
<i>EEE</i> .....	19	23	42
	<u>55</u>	<u>23</u>	<u>78</u>

One may note that symptoms were not produced in any of the thirty-six *AAA* observations. Of the forty-two instances with an *EEE* response, nineteen were not associated with symptoms and twenty-three were accompanied by some evidence of clinical intolerance. If chi-square is greater than 3.84 the observed difference would arise by accidents of sampling less than five times in a hundred; if greater than 6.65 the observed findings occur accidentally less than once in a hundred times. The finding of 16.08 indicates that the association of the *EEE* type of curve and the presence of allergic symptoms would occur as a result of chance alone less than once in ten thousand times.

When four-fold tables are prepared comparing the blood responses containing one or more *E*'s with the curves which do not contain an *E* in respect to the presence or absence of precipitated symptoms, one obtains the highly significant chi-square of 78.62.

	Without Symptoms	With Symptoms	
<i>E</i> .....	56	73	129
Without <i>E</i> .....	155	16	171
	<u>211</u>	<u>89</u>	<u>300</u>

On the basis of this finding and the general experience that a 10 per cent or greater leukopenia in any of the three post-ingestive counts is associated with an incompatible clinical reaction, this degree of leukopenia has been established as indicating a positive test. According to this definition, that is, the presence of a leukopenia of 10 per cent or greater, there were 129

positive tests in the series of 300 consecutive observations performed in allergic patients. Symptoms were precipitated during or following completion of the tests in seventy-three of the 129, or 56.7 per cent.

Various symptoms may be produced, including those previously illustrated, a reproduction of the allergic complaint or any of the minor objective or subjective manifestations outlined in Rinkel's recent article. It is imperative that the test subject be maintained under close observation, as minor changes in the symptoms, behavior and appearance of the patient are of clinical importance. It might be added that all the manifestations enumerated by Rinkel have been observed over a period of six years during which one of us (T. G. R.) has had daily experience with trial feeding techniques. We concur in the importance of looking for certain special manifestations during the course of the individual food tests, such as unexplained fatigue, drowsiness, chilliness, sweating, flushing or abdominal distress; these symptoms occur commonly and obviously may be overlooked if one is not alert to their clinical significance. Frequently symptoms are not produced within the first hour after the initial feeding but are promptly precipitated by the second feeding. This conforms with well-recognized observations in handling food-sensitive allergic individuals, but may not be appreciated unless one has had the experience of following their cases with carefully recorded food and symptom diaries. Telltale symptoms are sometimes delayed several hours, as in some of the cases illustrated; this is particularly true with an accentuation or recurrence of urticaria, eczema or diarrhea.

It should be noted that symptoms were not observed in approximately 40 per cent of the positive tests, that is, in the presence of a leukopenia of 10 per cent or greater. For several months all instances of this type were checked by cumulative feeding of the suspected food. Under such circumstances the diagnostic validity of the post-ingestive leukopenia as defined was usually upheld. As a result of efforts to check clinically both the positive and negative tests as determined hematologically, we have been impressed with the relative accuracy of the blood observations in detecting clinically offending foods even though the test feeding was not followed by the precipitation or association of symptoms. As experience with the method increases, one learns to respect the presumptive evidence of sensitivity afforded by the presence of a leukopenia in the absence of symptoms. This is a valuable criterion of current specific sensitivity in instances where diagnosis is most difficult, that is, where foods are responsible for symptoms because of their latent or cumulative action.

Not infrequently, however, one finds associated symptoms in the presence of leukopenia between 5 and 10 per cent (*D*) and occasionally when the decrease in leukocytes is less than 5 per cent (*C*). It must be pointed out that the symptoms are both objective and subjective and that particularly the latter may not necessarily be the result of an allergic reaction. From experience one learns that certain subjective symptoms usually indicate

# BLOOD STUDIES—RANDOLPH AND RAWLING

specific incompatibility and only those subjective manifestations commonly recurring and found to be of clinical importance are judged to be of significance. As previously mentioned, these reactive symptoms have been fully described in Rinkel's recent presentation. The factor of suggestion in relation to symptoms is controlled so far as possible in that the patient is given no indication of the results of the blood counts during the tests or for the remainder of the same day. It should also be stated that the majority of the tests were performed with the major allergens (wheat, corn, milk and eggs) for, as a rule in undiagnosed cases, specific sensitivity to these foods is not suspected due to the fact that they most commonly cause masked or cumulative types of reactions.

When the curves including an *E* in any of the three observations and a *D* in either the forty- or sixty-minute blood counts are compared with others one obtains a chi-square of 89.27.

	Without Symptoms	With Symptoms	
E or D.....	73	84	157
40 or 60			
Others .....	138	5	143
	<u>211</u>	<u>89</u>	<u>300</u>

Out of the 300 tests one is left with only five observations where significant symptoms were observed in the presence of a relatively flat type of blood response. Indeterminate hematologic findings occur between 5 and 10 per cent of tests; they may or may not be associated with evidence of clinical sensitivity and one must resort to cumulative test feeding after symptoms have been relieved to prove or disprove sensitivity in such instances.

In order to gain further information in this type of reaction, for a period of several months we performed total leukocyte counts at twenty-minute intervals for an hour after the second feeding, in addition to the standard routine. We encountered only an occasional instance of unquestioned clinical sensitivity where an absence of a 10 per cent leukopenia during the first period was followed by a diagnostic diminution of leukocytes after the second feeding. From this experience and the observation that telltale symptoms are so commonly produced immediately after the second feeding, we concluded that it is not necessary as a routine to perform additional leukocyte counts providing the patient remains under clinical observation for at least one-half hour after the second feeding.

The most significant observation to be drawn from these data is the fact that a trajectory type of post-ingestive leukocytosis has never been observed in the presence of allergic intolerance, as shown by the production of symptoms during or following the test or as a result of cumulative feeding immediately following this diagnostic procedure. This statement, again confirming Rinkel's observations, is based not only on the 300 tests tabulated in this survey, but also on an additional series of 1,500 other individual food tests. Under the terms of this procedure it may be said with safety that the presence of a trajectory type of post-ingestive

leukocytosis indicates specific allergic tolerance *at the time of the test*. The temporal aspect of this statement must be emphasized, for therein lies the greatest advantage of the individual food test, that is, its ability in detect-

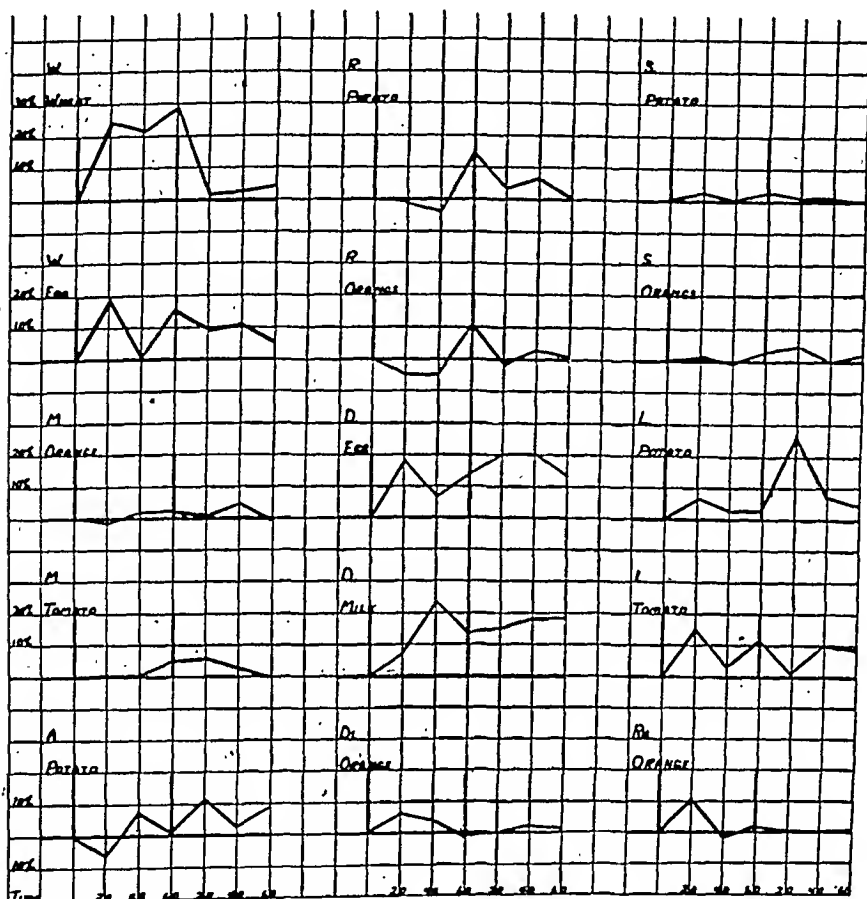


Fig. 6. The results of fifteen individual food tests in nine normal non-allergic individuals with total leukocyte observations at twenty-minute intervals after each of two feedings.

ing current tolerance or intolerance. The well-known clinical observations that tolerance to a specific allergen may be acquired as a result of avoidance or that a spread of sensitivity to a previously tolerated food may occur as the result of cumulative feeding, have been repeatedly observed and measured by this test technique.

It is inconceivable that the association of symptoms with the type of blood response as illustrated in these data could possibly occur by chance. The frequency of symptoms occurring in association with the incompatible blood response as judged by the definition of a leukopenia of 10 per cent or greater, and the absence of symptoms in the presence of a trajectory type of plotted curve, attest to the accuracy of this diagnostic method.

The major emphasis in the interpretation of the individual food test is placed on the symptom response, which is accentuated by the specific prep-

aration of the patient and by the administration of two doses of the test food. The presence of diagnostic symptoms is usually supported by the concurrent finding of a post-ingestive leukopenia. With symptoms of questionable significance the presence of a postprandial leukopenia is additional evidence in support of specific sensitivity. In the absence of precipitated or accentuated symptoms in association with test feeding one may assign diagnostic significance to various changes in the total leukocyte counts. The presence of a trajectory type of postprandial leukocytosis indicates current allergic tolerance for the tested food. A post-ingestive leukopenia of 10 per cent or greater in any one or several of the determinations is presumptive evidence of specific sensitivity. For these reasons, it is desirable to perform total leukocyte counts in association with experimental ingestion of the suspected food.

The identical technique with serial counts for sixty minutes after both the first and second feedings was carried out fifteen times in nine normal non-allergic individuals, each prepared by four days of specific avoidance prior to the test. The plotted results are shown in Figure 6. It should be observed that in no instance in this series did the total leukocyte count diminish more than 5 per cent from the basal pre-ingestion average. There were no symptoms even slightly suggestive of allergic intolerance following test feeding in these cases.\*

#### DISCUSSION

Although Vaughan's<sup>16,17,18</sup> subsequent publications and the early reports of Rinkel<sup>10</sup>, Zeller<sup>19</sup>, Rinkel and Gay<sup>12</sup> and Gay<sup>2</sup>, all in 1936 confirmed the value of the leukopenic index, Loveless, Dorfman and Downing<sup>3</sup>, and Brown and Wadsworth<sup>1</sup> published highly critical articles in 1938. Before discussing the objections of the latter authors, it should be emphasized that the current technique used by Rinkel and employed in the present study (except for minor variations mentioned) differs materially from earlier procedures in that the patient is tested to a food previously eaten regularly, then completely avoided for four days and tested on the fifth. This preparation of the patient accentuates both the clinical manifestations and the hematologic variations. Furthermore, the use of the individual food test as advocated by Rinkel and by us applies to the specific diagnosis of cases of unknown food sensitivity. As a general rule, allergic patients seek aid when having troublesome symptoms. Under such circumstances one may generally expect a higher incidence of reactive symptoms and a greater liability of the blood response than during periods of relative allergic balance.

Specific objections to procedures of this type have dealt principally with the question of the accuracy of total leukocyte determinations, with an apparent indifference to the wealth of clinical evidence of sensitivity which

\*Illustrative of the difficulty of selecting "normals" in this respect is the fact that Case R has developed unquestioned allergic reactions since this manuscript was submitted for publication. Allergic headaches have been experimentally induced on repeated occasions following ingestion of peanuts, beans and cauliflower.

is afforded by the observation of patients during the course of and immediately following individual eating tests. The high incidence of reactive symptoms associated with the trial feeding of foods, previously included in the diet but avoided for four days prior to the test, warrants the general use of this procedure. Quite aside from the controversy over the accuracy of the technique of leukocyte counting, the test feeding of specific foods is decidedly worth while from the standpoint of clinical observations afforded, whether or not serial leukocyte determinations are performed.

Loveless, Dorfman and Downing based their statistical analysis of the old leukopenic index on feeding tests with a group of non-allergic and a group of allergic individuals with known clinical food reactions. The blood response in the normals (their Group I) may be questioned, as they employed a test meal of wheat, milk and eggs instead of testing with individual foods. By using cases of known clinical sensitivity one might reasonably assume, at least from our experience, that these patients had been either avoiding the specific food for extended periods prior to the test or had been eating the questioned food in amounts not sufficient to produce symptoms and, thereby, were in a state of relative tolerance at the time of experimental testing. One certainly obtains the impression from the report of Loveless and coworkers that their test subjects did not submit themselves for relief of acute or chronic allergic manifestations at the time of the experimental observations. This is a very important point, and serves to emphasize the fact that their cases were selected on a different basis from that of the original or the current advocates of diagnostic feeding techniques.

The same criticism regarding the selection of allergic patients may be made in reference to the article of Brown and Wadsworth.

We observed similar difficulties when attempting to evaluate individual food tests in selected cases of known food sensitivity. Convincing clinical and hematologic evidence was not obtained until we started to study cases of uncontrolled allergy and adopted the routine of testing with foods previously eaten regularly but avoided for a short constant period prior to trial feeding.

The correct interpretation of the individual food test requires a working knowledge of the various phases of tolerance through which the food sensitive patient passes in respect to the length of specific avoidance. This knowledge is gained as a result of the detailed experience of handling food sensitive individuals by means other than the common but unfortunate practice of interpreting literally skin tests with food allergens. The findings of the individual food test are reproducible and the results are relatively easy to interpret if the factors of tolerance and the length of avoidance are constant as, for instance, in the observations of the present series.

The interpretation of food tests in cases of known sensitivity is fraught with hazard unless these variable factors are considered. A heterogeneous

group in this respect is not fit material for statistical analysis and from such a group conclusions concerning the reliability of the technique should not be drawn. It is imperative, therefore, that critics of techniques of this type attempt to use them in the sense employed by their advocates, namely, as diagnostic aids in studying food allergy instead of using this method to check cases of known sensitivity which, at the time, may be in various phases of clinical tolerance or intolerance.

It is by no means suggested that this is the only technique by which food allergy may be diagnosed. Basic elimination diets of the type recommended by Rowe<sup>13</sup> cannot be displaced, and there is no desire to do so. The chief practical value of the individual food test is the ability to detect current specific tolerance or intolerance to the foods which most commonly produce cumulative or latent reactions. The technique may be used to advantage in supplementing the basic type of elimination diets, either by testing of major suspects prior to the prescription of a comprehensive elimination plan or by checking questionable food following such a procedure.

Perhaps the greatest value of the individual food test pertains to the instruction of the patient and the physician. The clearcut demonstration of symptoms which so frequently occur under the circumstances of the test tends to convince the skeptical patient and insures a greater degree of co-operation in following a restricted diet than might otherwise be the case. Its routine use demonstrates many of the basic principles of food allergy dependent upon variations in specific tolerance, which otherwise are observed with greater difficulty.

#### SUMMARY

From a detailed study of 300 consecutive individual food tests performed in undiagnosed allergic individuals, we are able to confirm Rinkel's claim that the individual food test is a helpful and accurate aid in the current diagnosis of specific food sensitivity. Further experience with this method in the routine diagnosis of food allergy supports this conclusion.

It is to be emphasized that cases of undiagnosed clinical allergy were studied and that the specific food in question previously included in the diet, was eliminated for a period of four days prior to trial feeding. Testing patients in this phase of clinical intolerance materially accentuates the evidence of sensitivity as judged by the more constant production of symptoms in association with a diagnostic post-ingestive leukopenia.

Under the circumstances of this test there is a high degree of correlation between the presence of a post-ingestive leukopenia of 10 per cent or greater, and the production of symptoms of intolerance associated with test feeding or with evidence of specific sensitivity as a result of cumulative feeding. Symptoms suggestive of allergic intolerance occasionally occur with lesser degrees of leukopenia, but have not been observed in the presence of

a trajectory type of postprandial leukocytosis as a result of performing over 1,500 individual food tests.

\* \* \*

We are indebted to Dr. Frederic T. Jung, Associate Professor of Physiology, Northwestern University Medical School, for helpful suggestions regarding the mathematical treatment of data.

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THE IMMUNOCHEMISTRY OF ALLERGENS. VIII. Precipitin Formation and Passive Transfer Reactions with Allergenic Proteins from Cottonseed and Castor Beans. Colson, E. J., et al.; *J. Immunology*, 52:259, 1946.

The authors conclude from extensive experimental data that the allergenic proteic-polysaccharidic fractions from cottonseed and castor beans were precipitinogenic but that these fractions were less effective than ovalbumin in stimulating precipitin formation. Passive transfers are more sensitive for detecting serum antibodies than the precipitin method.

## ETHYLENE DISULPHONATE IN CHRONIC ASTHMA

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NEW theories concerning allergic diseases were presented in 1939 and 1940 by Evans, Bodman and Maisin.<sup>5</sup> They stated that the primary cause of allergy is a departure from normal in the chemistry of cellular metabolism involving the absence of certain catalysts of co-enzyme activity. An adequate supply of catalysts, making good the deficiency, would resolve the allergic state. They believed that the chemical energy produced and distributed by the metabolic activity of the living cell was essential for its normal function. Abnormalities of such metabolism involving an alteration in oxidation-reduction within the cells were believed responsible for the production of the allergic state. The changes could be due to shock, whether injective, traumatic or emotional, generally occurring in a person rendered susceptible by inherited tendency. The site and specific nature of cells affected would alone determine the type of allergy exhibited.

The fundamental need in the treatment of allergic state would be the recovery of the normal oxidation chain involved in the production and normal distribution of cell energy. This appeared to depend on the restitution of a normal carrier catalyst cycle by the provision of a substance (an oxidation catalyst) the absence of which is the direct result of the kind of trauma already referred to. A search by Evans and his co-workers for the substance led to the discovery of ethylene disulphonate, prepared by Endocrines-Spicer Ltd., of Watford, England. The drug was dissolved in triple-distilled water in pyrex glass containers and quickly sealed in ampoules, since the solution was considered to be highly unstable and rapidly oxidized in the presence of air, certain chemical substances, oil or grease. Recent observations reveal that the chemical will not disintegrate easily (Fig. 1).

The first laboratory investigation, which was reported, involved the use of thirty guinea pigs all of which were sensitized by two intraperitoneal injections (eight days apart) of Mercks crystalline egg albumin in doses of 0.1 gram. The animals were divided into two groups, namely A and B. Group A received 1 c.c. of the solution of ethylene disulphonate and Group B acted as a control. Three hours later all animals were given a shocking dose of 0.8 gram of egg albumin. There were no deaths in Group A, but in Group B one-third of the animals died. The same protection was still present if the shock dose was administered twenty-four, forty-eight or seventy-two hours after the drug was injected.

Another animal experiment was conducted. Group A now was given

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## ETHYLENE DISULPHONATE—BRENNER AND STOESSER

three doses of 1 c.c. of the ethylene disulphonate solution at eight-day intervals. Two months after the last injection, the animals of both groups received a shocking dose of 0.8 gram of egg albumin with the result that 33 per cent of Group A died and 95 per cent of Group B.



Fig. 1. A small supply of ethylene disulphonate. Before the material is dissolved in water, it appears to be quite stable.

Smith<sup>11</sup> of this country made a study with twenty guinea pigs. He sensitized the animals with egg albumin as described by Evans, Bodman and Maisin. Twenty-eight days following sensitization, one-half of the guinea pigs were injected intraperitoneally with 1 c.c. of the solution of ethylene disulphonate and three hours later all the animals were given a shocking dose of egg albumin. Two of the treated animals succumbed while none of the controls lived.

Fisk, Small and Foord<sup>7</sup> using a large number of guinea pigs and the same procedures had a mortality rate of 60.61 per cent among thirty-three animals receiving ethylene disulphonate, 67.74 per cent among thirty-one guinea pigs which were given distilled water and 72 per cent among animals untreated and acting as controls. The authors concluded that the differences were within the limit of standard error and the odds were due to chance. They could not confirm the work of Evans and his associates, nor that of Smith.

The English investigators also carried out some clinical studies. After preliminary experimentation they decided that the best results would be obtained if the individuals receiving ethylene disulphonate were given a special routine of preparation. Each patient was required to drink over a period of five minutes one quart of warm or cold water containing two level teaspoons of salt one-half hour before breakfast for three consecutive mornings. Bilisolin (Endocrines-Spicer Ltd.) was recommended for five days or until free bile appeared in the stool. Drugs such as morphine, barbiturates, alcohol, tobacco and aspirin were withheld for one

# ETHYLENE DISULPHONATE—BRENNER AND STOESSERT

TABLE I. SEVENTY-ONE CASES TREATED BY EVANS, RODMAN AND MAISIN

No. Injections Ethylene Disulphonate	Complete Control of Allergic Symptoms		Partial Control of Allergic Symptoms		No Change	
	No. Cases	Per cent	No. Cases	Per cent	No. Cases	Per cent
One	7	9	8	11	2	3
Two	8	11	17	24	0	0
Three	4	6	23	33	2	3
Total	19	26	48	68	4	6

week before and three weeks after an injection of the ethylene disulphonate solution. The diet of the allergic patients was made high in vitamins B<sub>1</sub>, B<sub>2</sub>, and C. No meat was permitted for one week prior to an injection and three weeks thereafter.

The technique of administration of the solution of ethylene disulphonate was carefully controlled by Evans and his co-workers. The skin was cleaned without using a disinfectant. The drug was quickly drawn from the 2 c.c. ampoule into a syringe, a needle attached and an injection made rapidly into the triceps muscle.

This form of therapy gave favorable results in 94 per cent of the patients as shown in Table I.

Smith<sup>10</sup> carried on the clinical work. In 1942 he reported upon a group of thirty-three allergic adults including twenty-five individuals suffering from asthma, six with asthma who exhibited urticaria and eczema, one patient with migraine, and one case of "skin manifestation." Successful results were obtained in 82 per cent of the patients and another 8 per cent were greatly relieved.

Wasson<sup>12</sup> studied forty children with asthma, eczema, hay fever, urticaria or any combination of these conditions and presented the results in 1943. The author gave twenty patients the ethylene disulphonate solution, the remainder acting as controls. Completely relieved were eleven children receiving the drug, while among the controls six cases received satisfactory results from other forms of therapy.

Bartlett<sup>2,3</sup> reviewed his cases and published the work in 1944. He had excellent results among 247 children and fairly good relief among 528 adults, which led him to conclude that the treatment of the allergic state with ethylene disulphonate is a decided advance in therapy. This conclusion was given further support by the report of Feder and Tribble.<sup>6</sup> They also had favorable results when using the drug and felt it was a new hope for the allergic.

Recently, however, less favorable reports have appeared. Archibald<sup>1</sup> observed forty-five children over a fairly long period of time and in his publication of 1945 he states that the use of ethylene disulphonate in-

icates a non-specific form of treatment which although occasionally very beneficial in the allergic individual is disappointing in the long run. Kurland and Bubert<sup>8</sup> made a thorough investigation in a small group of adults. They followed as closely as possible the recommendations of

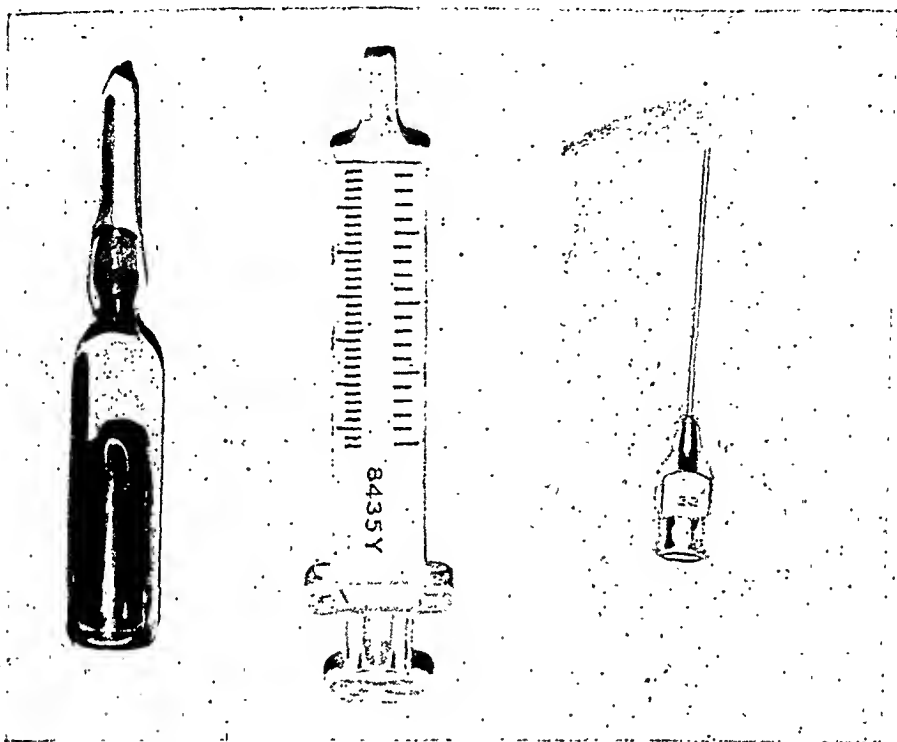


Fig. 2. One 2 c.c. size ampoule of ethylene disulphonate (Allergosil Brand) in a dilution of 10-15 in triple-distilled water with the specially cleaned syringe and needle furnished by the manufacturer.

Evans, Bodman and Maisin and treated twelve cases of asthma with the drug. Observations were made over an average of seventeen weeks and it was found that ten patients gave no response and two showed some improvement. As a result these investigators concluded in their preliminary report of 1945 that the claims for ethylene disulphonate are completely excessive.

The present study of the therapeutic value of ethylene disulphonate was made in a selected group of fifteen cases with chronic asthma. All the individuals were receiving treatment based on complete diagnostic procedures. Offending foods were eliminated from the diet, irritating inhalants were avoided, and in some instances foci of infection were removed. Little improvement occurred and the patients were admitted to the hospital where there was no change in symptoms.

Each case was prepared for the administration of the ethylene disulphonate as recommended by the manufacturer. An adequate diet of normal

# ETHYLENE DISULPHONATE—BRENNER AND STOESSER

TABLE II. TEN CASES OF CHRONIC ASTHMA RECEIVING ETHYLENE DISULFONATE

Case No.	Sex	Age	Yrs. of Asthma	Injection of Ethylene Disulphonate	Results
1-EC	F	26	4½	3 injections one day apart and one 6 weeks later	Poor
2-RS	M	70	60	2 injections 2 weeks apart and one 6 weeks later	Fair
3-JW	M	51	9	2 injections 2 weeks apart and one 6 weeks later	Poor
4-GW	F	26	7	2 injections 2 weeks apart and one 6 weeks later	Poor
5-VV	M	68	7	2 injections 2 weeks apart and one 9 weeks later	Fair
6-EH	F	31	13	2 injections 2 weeks apart and one 6 weeks later	Poor
7-WM	M	56	10	2 injections 2 weeks apart and one 9 weeks later	Poor
11-JR	M	37	30	2 injections 2 weeks apart and one 6 weeks later	Poor
14-AN	F	54	20	2 injections 2 weeks apart	Poor
15-CP	F	42	38	2 injections 2 weeks apart	Good

TABLE III. FIVE CASES OF CHRONIC ASTHMA RECEIVING TRIPLE-DISTILLED WATER

Case No.	Sex	Age	Yrs. of Asthma	Injection of Ethylene Disulphonate	Results
8-JH	M	66	35	2 injections 3 weeks apart and one 9 weeks later	Good
9-JC	M	52	26	2 injections 2 weeks apart	Fair
10-FS	M	63	5	2 injections 2 weeks apart	Poor
12-HS	M	76	12	2 injections 2 weeks apart	Fair
13-JO	F	30	9	2 injections 2 weeks apart and one 6 weeks later	Poor

energy value was provided. No meat was permitted for one week before and three weeks after the injection of the drug. Sugar was reduced in the diet by avoiding the use of refined or raw sugar in foods or drinks, and this loss in calories was replaced by giving more whole cereal grains. Vitamins B<sub>1</sub>, B<sub>2</sub>, and C were kept at a high level.

The bowel was washed through by causing each patient to drink one quart of cold or warm water containing two level teaspoonfuls of common salt, half an hour before rising. The whole quart was drunk within five minutes. The procedure was carried out for three consecutive mornings and then once weekly.

Alcohol, aspirin, barbiturates, sulfonamides, opium derivatives, and tobacco were omitted during the entire period of the investigation.

After a week of preparation, the first injection of one 2-c.c. ampoule of ethylene disulphonate (Allergosil Brand)\* in a dilution of 1.10-15 in triple-distilled water was made in ten cases, and of sterile triple-distilled water in five cases which acted as controls. The manufacturer's technique of injection was followed in all patients and is here presented (Fig. 2).

"The skin is cleaned by rubbing with sterile wool. No disinfectant may be used. The syringe is then assembled and the neck of the ampoule removed, the contents being drawn into the syringe. Then (and not until then) the needle is placed in position. The injection is then made deep into the triceps, or deltoid, muscle.

\*Obtained from Spicer-Gerhart Company of Pasadena, California, by the Food and Drug Administration, Federal Security Agency, Washington, D. C., and sent by registered mail to the authors who used the drug before the expiration date on each package.

## ETHYLENE DISULPHONATE—BRENNER AND STOESSER

The object should be to introduce the material from the ampoule to the muscle as rapidly as possible and with as little exposure as possible to air and metal. After the injection, watch until a natural seal of the puncture has taken place. No applications whatever are to be used except pressure with sterile, dry cotton wool."

Further injections of the solution of ethylene disulphonate or the triple-distilled water depended upon the progress of each case. Hospitalization afforded an opportunity to watch all patients carefully. Records of all complaints were made and physical examinations were performed frequently.

The results are summarized in Tables II and III.

All the patients receiving the ethylene disulphonate solution experienced muscle fibrillation and some pain after the injections. The first patient was made worse by the drug while the second felt better in spite of little change in physical findings. However, after three months, the asthma returned with frequent severe attacks. The improvement in the third case continued for ten days after which bronchopneumonia developed and the asthma was made worse. The fourth, sixth and seventh cases were complete failures. The fifth patient had less complaints and there was improvement on physical examination. Case eleven revealed marked muscle fibrillation and much pain. He did poorly. The next patient was relieved for only one week, but the last patient had a more lasting improvement. She was very enthusiastic over the treatment for many months.

There was also muscle fibrillation and pain in association with the injection of triple-distilled water. The first case of this group had a satisfactory response. After a second injection of the distilled water he had only one attack of asthma each week instead of the usual daily one. Two more patients, namely, nine and twelve, showed improvement, with patient nine expressing definite relief while the other patient revealed physical findings of less asthma. The remaining two patients did not respond; in fact, the last patient was made worse and objected to the triple-distilled water injections.

The chronic asthmatic patients of this study received the best of care. All known methods of diagnosis and therapy were employed and in spite of all this work, the symptoms continued. Ethylene disulphonate was considered on account of early favorable reports.<sup>5,11</sup> Ten patients received the drug and five others were given triple-distilled water. All rules and regulations requested by the manufacturer of the ethylene disulphonate solution were followed. This was possible because of the fact that the patients were in the hospital and could be watched continuously.

The results from the use of the drug were far from satisfactory. The small series of patients chosen gave an opportunity to study the effect of ethylene disulphonate closely and under these circumstances only a few

of the cases receiving the drug showed a good response. The same picture was revealed by the patients receiving plain distilled water, a form of therapy first tried several decades ago.<sup>9</sup>

The clinical effects of ethylene disulphonate and triple-distilled water are similar. Any favorable action is not specific. The possibility of a psychological reason for the results may be considered but in the present investigation was not confirmed. The most neurotic patients did not respond satisfactorily to the drug or the water therapy. There still may be a physiological stimulation but this is not necessarily due to ethylene disulphonate.<sup>4</sup>

#### CONCLUSIONS

An intensive study of the use of a solution of ethylene disulphonate (Allergosil Brand) in a small group of chronic asthmatic hospital patients showed that the drug is of little value.

The results were no better than those obtained from the administration of triple-distilled water.

If the few favorable responses from both forms of treatment are not based on a psychological background, then there may be other reasons, the thought of which warrants further investigations of the whole field of non-specific therapy in allergic diseases.

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# PENICILLIN DERMATITIS BASED ON TUBERCULIN-TYPE SENSITIVITY

## Report of a Case with Remarks on Experimental Sensitization to Penicillin

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**R**EPORTS of allergic sensitization from penicillin are increasing. The following case of local sensitization through external contact with penicillin is reported because it appears based on tuberculin-type sensitivity.

### CASE REPORT

The patient, a nurse twenty-six years of age, presented herself September 11, 1945, on account of a vesicular dermatitis involving several fingers of both hands. This eruption originated about six months ago, shortly after penicillin treatment was introduced at the hospital where the nurse worked. The dermatitis began with little blisters on several fingers. The patient remembers that she spilled some of the solution over her fingers. The eruption cleared up on several occasions when the nurse was off duty, and also at the hospital when she kept away from penicillin.

On examination a slight vesicular eruption on several fingers of both hands was noted. The results of the general examination were irrelevant. Routine patch tests with common contacts including soaps were negative. Intradermal tests with various mycotic and bacterial antigens gave a 2+ reaction to trichophyton, 3+ to oidiomycin, and minor reactions to staphylococcus and streptococcus; the latter not different from those usually elicited in adults. The patient had suffered previously from a dermatophytosis of the feet which accounted for the positive trichophyton reaction. Intradermal tests with commercial mold antigens of penicillium notatum, penicillium glaucum and aspergillus were negative.

### TESTS WITH PENICILLIN

Intradermal tests with penicillin regularly produced a tuberculin-type delayed reaction. Tests were carried out and repeated with sodium penicillin (Lilly), and calcium penicillin (Winthrop); 250 to 1,000 units contained in 0.05 or 0.1 c.c. of normal saline solution were used. An intradermal test with crystalline sodium penicillin "G", containing 500 units (0.3 mgm.) gave the same positive result.

There was no true urticarial reaction, although a small wheal appeared at all sites immediately; but this was not different from the wheal occurring in non-sensitive controls. However, about ten to twelve hours later a delayed reaction appeared, with a maximum of about twenty-four to forty-eight hours, presenting itself as a tuberculin-type infiltrated itching lesion.

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## PENICILLIN DERMATITIS—EPSTEIN AND PINKUS

of from 1.2 to 1.8 cm. in diameter (Fig. 1, right side. Left side shows negative controls on the arm of a different patient).

The histologic picture of such a reaction examined twenty-four hours

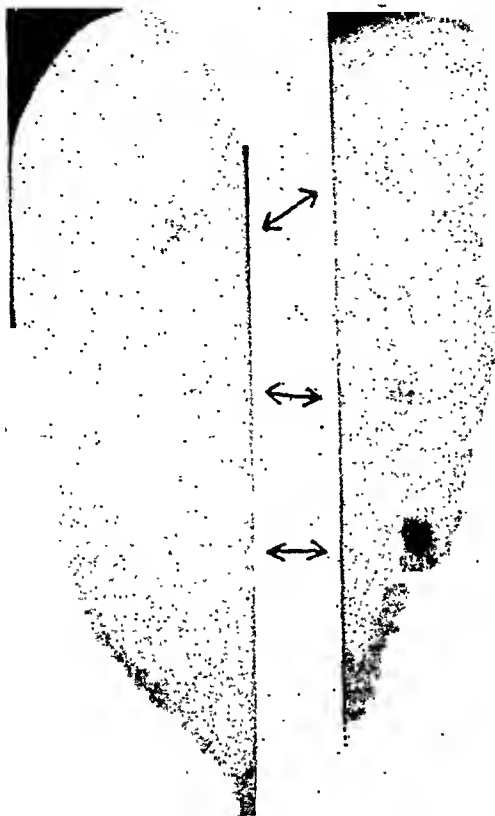


Fig. 1. Tuberculin-type reaction to different commercial penicillins after forty-eight hours (right side of picture). Note completely negative controls on the arm of a normal volunteer (left side of picture; arrows point in their direction).

after the injection of the penicillin was that of a localized cutaneous inflammation (Fig. 2), typical of a "tuberculin type" response:

"The epidermis is practically normal. The corium shows edema and diffuse increase of fixed connective tissue cells with swollen nuclei. The blood vessels are filled with polymorphonuclear cells and surrounded with dense sheaths of lymphocytes. The center of the pathologic reaction is in the mid-corium. No eosinophiles are found. Mast cells are present in average numbers."

This tuberculin-type reaction persisted for some time. The infiltration subsided and eventually turned into a superficial eczema-like lesion which presented itself three weeks later as a mild dermatitis. The biopsy at that time presented the picture of a subsiding mild dermatitis:

"The epidermis is acanthotic, about twice the normal thickness and slightly ede-

## PENICILLIN DERMATITIS—EPSTEIN AND PINKUS

matous. The edema is mostly intracellular. Keratohyalin and keratin layers are normal except in one relatively small area which is parakeratotic with loss of the granular layer. However, there are several areas where a parakeratotic scale



Fig. 2. Microscopic appearance of tuberculin-type reaction as presented in Figure 1. Note edema of corium and lymphocytic, largely perivascular infiltrate.

is superimposed on the normal horny layer. There is barely any cutaneous edema, but the subpapillary blood vessels have thickened walls and show mild perivascular sheaths of round cells."

*Patch tests*—Numerous patch tests with penicillin performed on normal skin of the arms and legs of the patient, in solution as well as with dry commercial penicillin powder, were negative. Patch tests on fingers that had not been affected previously were also negative. However, when a patch test with a few drops of a penicillin solution containing 5,000 Oxford units in 1 c.c. was performed on the patient's fingers at a site that previously had shown an eruption, itching was noted within three hours. At that time a localized eruption consisting of small pinpoint to pinhead sized vesicles was noticed. The vesicles increased somewhat in size. After twenty-four hours a picture of "dysidrosis," an eruption of clear vesicles, was present (Fig. 3).

A biopsy of this vesicular eruption taken twenty-four hours after the application of the penicillin solution showed the typical picture of a "dysidrosis" type of dermatitis (Fig. 4, A and B):

"The typically thick epidermis of the finger shows spotty edema, spongiosis and vesiculation in different levels. Upon closer scrutiny one finds that most of the vesicles and areas of spongiosis are connected with ducts from sweat glands.

## PENICILLIN DERMATITIS—EPSTEIN AND PINKUS

There is considerable transmigration of leukocytes which partly disrupts the epidermal structure. The papillae and the subpapillary layer are highly edematous and show lymphocytic infiltration around the widened blood vessels which contain polymorphonuclear leukocytes. Eosinophiles are absent.”\*

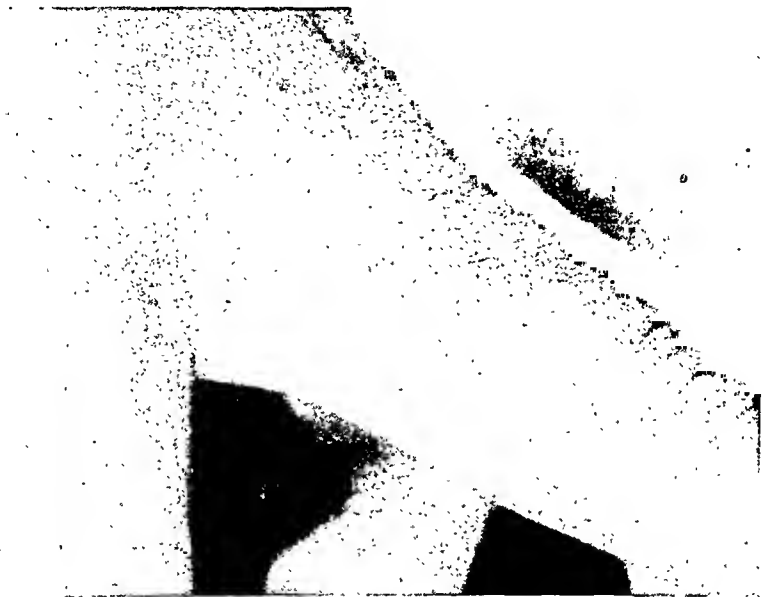


Fig. 3. Vesicular "dysidrotic" eruption of finger, twenty-four hours after application of commercial penicillin. A few drops of a solution containing 5000 units per 1 c.c. were applied for three hours.

A patch test with penicillin at the site of a former positive intradermal test produced redness after eighteen hours, but no blisters and no pruritus.

### PASSIVE TRANSFER

Passive transfer of the sensitivity was attempted on four volunteers. The results were completely negative in three instances. In the fourth instance a slight redness about 5 mm. in diameter was noticeable after twenty-four and forty-eight hours at both sites tested. Although the control sites did not react, the evidence does not seem great enough to be definitely considered a positive passive transfer.

### EXPERIMENTAL SENSITIZATION TO PENICILLIN

Of the four volunteers that were used for controls and passive transfer, two became sensitized to commercial penicillin. Only one of them was available for further study. He had received four intradermal injections

\*We are indebted to Professor Felix Pinkus, Monroe, Michigan, for the preparation of the microphotographs.

of penicillin. Six days after the passive transfer test, he noticed severe itching at some test sites. At one of them an inflammatory wheal about 1 cm. in diameter with a flare one inch in diameter was present. Half



Fig. 4. (A) Vesicular "dysidrotic" dermatitis of finger following local application of penicillin. The vesicles apparently are located at the site of sweat gland ducts. One of these ducts leading down from the vesicle at the extreme right can be recognized in the papillary and subpapillary strata (see arrows). (B) There are flat shaped vesicular spaces above the middle vesicle possibly corresponding to the enlarged intra-epithelial part of a duct (see arrow). The connection of the large vesicle at the left side with the duct of a sweat gland was apparent from other sections.

an hour later a similar inflammatory, somewhat urticarial swelling with itching appeared at two more test sites, and several hours later the last test site showed a similar, though smaller, lesion. Twenty-four hours later

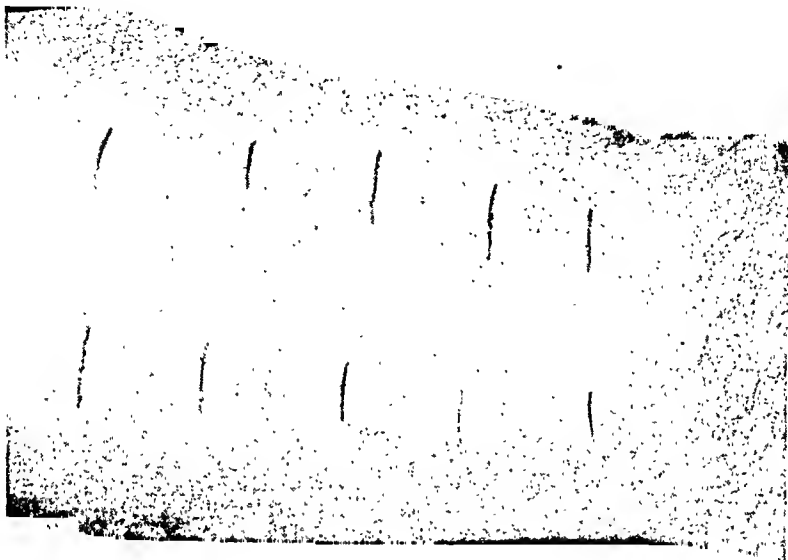


Fig. 5. Tuberculin-type reactions to various commercial penicillins in volunteer who had become sensitized following attempts at passive transfer. The sites where penicillin was combined with serum (see page 189) reacted earlier and more severely after twenty-four hours (upper row, sites 1 and 4, lower row, site 2 from the left). This picture was taken forty-eight hours after the test. At that time the differences had become less pronounced.

there was a definite reaction at all four sites which had received penicillin. Henceforth, all further injections of commercial penicillin (125 units to 500 units) produced tuberculin-type reactions (Fig. 5). They appeared within ten to eighteen hours and were accompanied by itching. These lesions began fading after forty-eight hours and turned into a superficial dermatitis which was present for two weeks.

Microscopic examination of such an experimental lesion twenty-four hours after the injection showed an acute localized inflammation of the corium corresponding to the tuberculin-type reaction:

"The epidermis is normal. At one spot in mid-corium there is a small hemorrhage and the whole surrounding area is diffusely infiltrated with grotesquely shaped nuclei, probably very actively motile leukocytes and possibly lymphocytes. Other areas show narrow blood vessels which contain polymorphonuclear leukocytes and are surrounded by fairly heavy round-cell infiltration."

Another biopsy from a similar lesion was taken at a later stage, sixty hours after the injection. It presented the picture of a subacute, non-

specific inflammation of the corium (Fig. 6, *A*) plus an early "eczematous" reaction of the epidermis (Fig. 6, *B*):

"Most of the epidermis is normal, but there are some areas of spongiosis and a

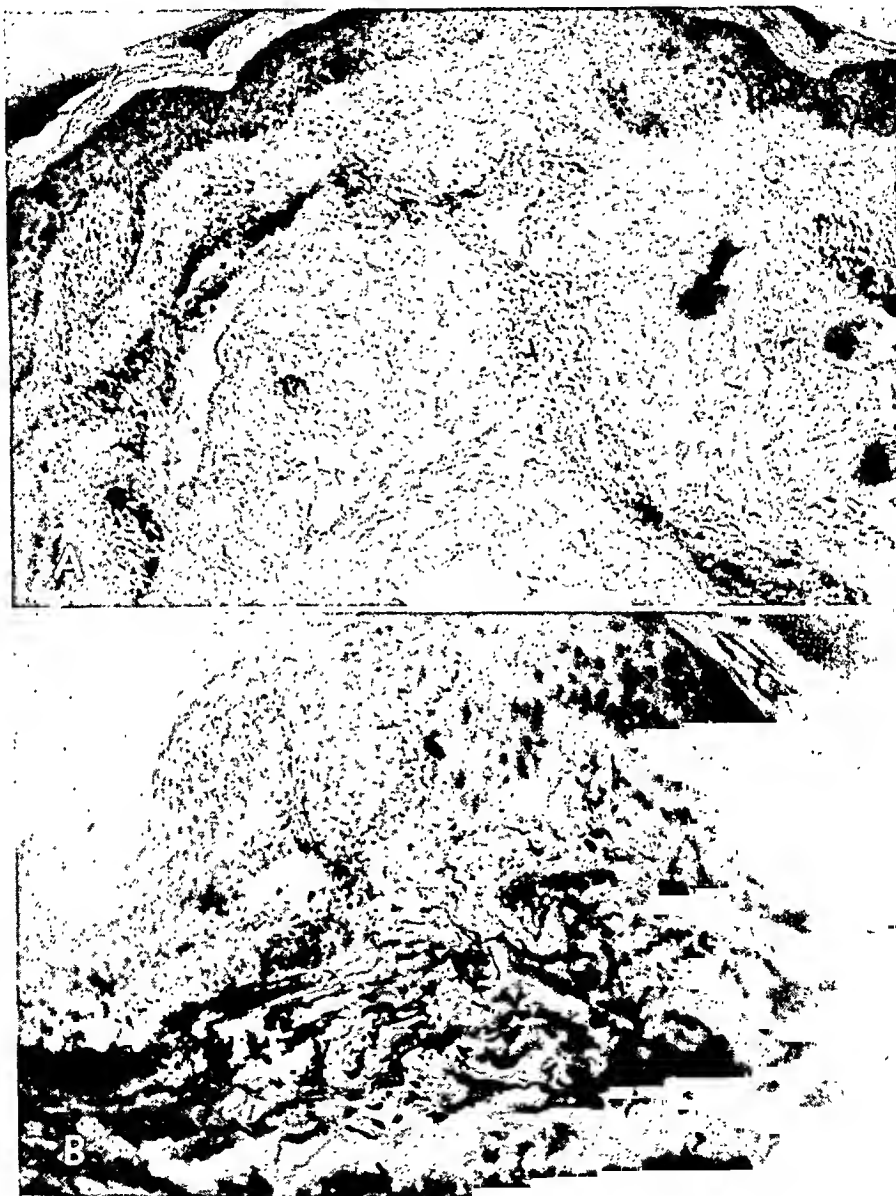


Fig. 6. (*A*) Tuberculin-type reaction from commercial penicillin in a volunteer. Biopsy taken after sixty hours. Non-specific inflammation of the corium. Most of the epidermis is intact. (*B*) Same lesion, different section. This picture shows one of the few areas with epidermal changes. Transmigration of leukocytes into the epidermis and "spongiosis" (at center and left side of the microphotograph).

few small vesicles. The horny layer is normal throughout. Practically all the blood vessels of the upper half of the corium are sheathed in rather heavy round-cell infiltrates. The vessels themselves are wide and filled with red cells. There is no unusual number of polymorphonuclear cells."

# PENICILLIN DERMATITIS—EPSTEIN AND PINKUS

TABLE I. TUBERCULIN-TYPE SENSITIVITY VERSUS ECZEMATOUS CONTACT-TYPE SENSITIVITY

Type of reaction:	Tuberculin-type or Microbic-type reaction	Contact-type or "eczematous" reaction
Clinical lesion:	Papular lesion	"Eczematous" dermatitis
Pathologic characteristic:	Inflammatory	Inflammatory
Time of appearance of reaction:	"Delayed" (after 8 to 48 hours)	"Delayed" (after 8 to 48 hours)
Shock Organ:	Cutis	Epidermis
Antibodies:	Only fixed antibodies	Only fixed antibodies
Release of histamine or histamine-like substance:	Not demonstrated	Not demonstrated
Result of <i>in vitro</i> antigen-antibody reaction:	Damage to cells	Damage to cells
Relation of site of test to intensity of reaction:	Reaction stronger the closer to primary focus	Reaction stronger the closer to primary focus
Eosinophilia	0 or +	0 or +
Heredity	?	?

Intradermal tests with 250 to 1,000 units of crystalline sodium penicillin "G" did not produce any pathologic reactions. Unlike the original patient, this volunteer had not become sensitized to the crystalline penicillin, but to some impurity of the commercial products.

## DISCUSSION AND COMMENTS

**Immunologic Aspects of the Case**—The case presented is interesting on account of the particular immunologic response of the skin. One might be inclined to classify our case as a contact dermatitis. Instances of local sensitivity of the skin from contact with penicillin have been reported previously, the first one by Pyle and Rattner.<sup>2</sup> These authors presented a true case of contact-type dermatitis. According to our present concepts, "contact-type" dermatitis is usually based on a delayed "eczematous" reaction of the epidermis, as evidenced by a positive eczematous reaction to a patch test. There can be no doubt that external contact was the cause of the dermatitis in our case. However, it is the type of reaction and the shock organ that determine "contact-type dermatitis," and not the avenue of the allergen. The latter may be brought in contact with the shock organ from without and within. Conversely, not all dermatitis that is brought about by external contact is immunologically "contact-type dermatitis." Our case seems based on the tuberculin-type of sensitivity and not the ordinary eczematous contact-type sensitivity. A comparison of tuberculin-type sensitivity and "eczematous" contact-type sensitivity is presented in Table I.

It becomes apparent from this table that tuberculin-type sensitivity and "eczematous" contact-type sensitivity share many characteristics. They

differ mainly in regard to the shock organ. Perhaps these two forms are identical in principle. In tuberculin-type sensitivity the shock organ is mainly the cutis; in eczematous contact-type sensitivity, chiefly the epidermis. That would account for their frequent association.<sup>†</sup> Still the difference of the shock organ constitutes reason enough for the distinction of the two types of sensitivity.

Tuberculin-type sensitivity to penicillin had been demonstrated previously by Rostenberg and Welch.<sup>4,5</sup> However, Rostenberg and Welch's patients did not suffer from a dermatitis. Our case represents an actual penicillin dermatitis based on tuberculin-type sensitivity. The patient responded with a papular cutaneous reaction to intradermal injections of penicillin. The existence of the tuberculin-type sensitivity was verified by the histologic study (Fig. 2). The negative patch tests with penicillin demonstrated the lack of general contact-type eczematous sensitization. The local application of penicillin to the previously diseased finger produced a vesicular "dysidrotic" dermatitis.

This is evidence of some localized epidermal sensitivity in addition to the underlying tuberculin-type cutaneous sensitivity. This observation seems to contradict the claim that the patient's dermatitis is based on tuberculin-type sensitivity. One might assume that this is an instance of true localized eczematous contact dermatitis, and the general tuberculin-type sensitivity may be just incidental. Such a conclusion is not warranted. Involvement of the epithelium does not necessarily make a dermatitis a "contact-type" dermatitis. I may recall that the superficial trichophytosis of the glabrous skin always produces epidermal changes in the form of spongiosis, frequently leading to intra-epithelial vesicles. Yet the generalized sensitivity in these cases usually is of the tuberculin type.

Our assumption that our case is based on tuberculin-type sensitivity rests also on the fact that the clinical picture corresponded perfectly to the vesicular dermatophytid of the hands which we see so often in patients with dermatophytosis of the feet. In both instances we find a grouped vesicular eruption, not a diffuse dermatitis. In both instances the lesions are located mostly around sweat ducts. In both instances there is a generalized tuberculin-type (dermal) hypersensitivity but no generalized epidermal sensitivity. In both instances there is a tendency to very localized epidermal sensitivity. In our patient, application of a penicillin solution produced an eruption only on previously affected fingers, and not on others. The tendency of some dermatophytids to recur regularly at the same sites is known.

<sup>†</sup>Co-existing epidermal and non-atopic dermal sensitivity are encountered much more often than is generally recognized. It is not the purpose of this paper to go into general theoretical principles. However, their discussion is of great theoretical and practical importance in regard to certain forms of eczema, notably contact-type dermatitis and microbial (bacterial and fungus) eczemas. Studies on non-atopic dermal sensitivity, their implications and explanation, will be presented in forthcoming publications by one of us (S.E.): Studies in contact-type dermatitis.—I. Role of non-atopic dermal hypersensitivity in contact dermatitis.—II. "Dermatitis": Dermatitis based on non-atopic dermal hypersensitivity.—III. Identity of dermal non-atopic sensitivity and tuberculin-type sensitivity. (To be submitted to the *Journal of Investigative Dermatology*).

## PENICILLIN DERMATITIS—EPSTEIN AND PINKUS

These parallels justify the classification of our case as a dermatitis based on tuberculin-type sensitivity. It seems probable that some of the vesicular id-like eruption encountered not infrequently in sensitivity to parenteral penicillin<sup>1</sup> can be explained on the same basis. There exists also a practical angle. Our case demonstrates that one may deal with a dermatitis by local contact where patch tests may be negative on normal skin. The generalized tuberculin-type sensitization demonstrates that this was not just a matter of local sensitivity. Such an occurrence apparently is not unique. Similar observations have been made with other "contact" allergens, notably drugs.‡

### REMARKS ON EXPERIMENTAL SENSITIZATION TO PENICILLIN

The accidental experimental sensitization to penicillin observed in the volunteers who submitted to the passive transfer test confirmed largely the experiences of Rostenberg and Welch<sup>5</sup>, although their cases became sensitized to crystalline penicillin, whereas our volunteer apparently became sensitive to some impurity of the commercial penicillin. Our experiments also indicated that the preceding injection of blood serum enhanced both the chance of sensitization and the degree of reaction, as had been noted by Rostenberg and Welch.<sup>5</sup> Out of the four volunteers for the passive transfer, two became sensitized. Furthermore, in the sensitized person injections of serum and penicillin led to an earlier appearance and a more intensive reaction than injection of penicillin alone. Whether serum and penicillin were injected simultaneously or whether the penicillin test followed the serum injection by twenty-four hours made no difference. The stimulating effect of homologous serum on sensitization to drugs is known from previous experiments of Frei and Landsteiner, who demonstrated that guinea pigs could be sensitized much more easily to neoarsphenamine when the drug was mixed with guinea pig serum. The relative ease of sensitization to penicillin by intradermal injections, especially in conjunction with serum injections, should caution against indiscriminate skin testing with this drug. When passive transfer is attempted, the recipients should be warned about the danger of sensitization because sensitization to penicillin may be a great handicap to the sensitized person.

### SUMMARY

A case of a vesicular dermatitis of the hands due to external contact with penicillin is presented. The patient was generally sensitized to penicillin, both commercial brands and crystalline penicillin "G". Only intradermal

*(Continued on Page 220)*

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‡In these instances also patch tests were negative, but severe tuberculin-type cutaneous reactions to the same allergens could be demonstrated. These observations will be reported elsewhere (see footnote†, page 194). They should teach us that a negative patch test to a substance cannot be trusted when the clinical picture or course suggests hypersensitivity to the same agent. As a word of warning, I may add that if intradermal tests with contact allergens are performed, much weaker concentrations must be used than for patch testing. For instance, for nickel sulfate a 5 to 10 per cent aqueous solution is recommended for patch testing (3); for intradermal tests 0.02 c.c. of a 1:40,000 dilution in normal saline appears the proper dose.

## REACTIONS TO PENICILLIN

GEORGE W. TRUITT, M.D., F.A.C.A.  
Chadds Ford, Pennsylvania

AS has been so well stated by Brown<sup>3</sup> recently, the reactions to penicillin now are beginning to pour in with its more widespread use. He quotes Pyle and Rattner<sup>9</sup> as describing a contact dermatitis occurring in a medical officer who prepared and administered penicillin solution. There was marginal conjunctivitis spreading to the bridge of the nose and forehead and the central portions of the face with eczematous lesions on the hands and penis. All eruptions disappeared on cessation of contact and reappeared as soon as re-exposure occurred. Patch tests were strongly positive.

Brown<sup>3</sup> also reviews the following cases: One, a chemist described by Silvers<sup>11</sup> was engaged in research. An itchy rash appeared on the eyelids and penis after one year's exposure with complete disappearance as soon as direct contact with penicillin ceased. Brinkley and Brockmole's<sup>2</sup> patients were both physicians handling penicillin. In one, the eruption appeared on the forehead and forearms with a positive patch test. In the second the rash was thought to be a seborrhoeic dermatitis. Patch test here was negative but eruptions of hands and feet occurred following an injection of 60,000 units. In both cases eruption disappeared on avoidance of contact with the drug. Barker<sup>1</sup> describes a medical officer dispensing penicillin solution. The lesion was an acute dermatitis of the face and neck. His second case responded to penicillin injections with dermatographia plus large confluent wheals on trunk and extremities. In both cases patch tests reproduced the original lesions. Freyhan's<sup>5</sup> patient developed a severe generalized pruritus for five days after 100,000 units of penicillin over a period of ten days. Crip's<sup>4</sup> case developed a generalized urticaria after 200,000 units over fourteen days. On this patient direct intradermal skin tests, passive transfer and precipitin tests were positive with penicillin solution.

Keefer<sup>7</sup>, writing in 1943, remarks: "One of the remarkable features of penicillin is its low toxicity and the extremely low incidence of a systemic nature." In 500 cases, urticaria was reported in only fourteen cases with thrombophlebitis (at the site of injection) and occasionally chills and fever. Writing again on this subject in 1945, Keefer<sup>6</sup> mentions urticaria in 2 to 5 per cent and occasionally attacks of vesicular eruptions. He states: "At present we have seen one severe rash of this type: There are no known contra-indications to the administration of penicillin." Lyons<sup>8</sup> found three types of complication to penicillin therapy. First, urticaria in 5.7 per cent of 209 cases. This usually occurred during the course but could come on as late as nine days after treatment. He found that subsequent courses of treatment with penicillin in these patients

## REACTIONS TO PENICILLIN—TRUITT

who developed urticaria were uneventful and not associated with a recurrence of the skin lesion. With the urticaria may appear abdominal cramps and fever. Secondly, transient azotemia and thirdly, thrombophlebitis was frequent at the site of I.V. injection.

Rotenberg and Welch<sup>10</sup> found that 5.5 per cent of 144 individuals who had no previous contact with penicillin reacted with a tuberculin type of lesion when given 1/10 c.c. containing 1,000 units of penicillin intradermally.

They then injected intradermally nine patients with 10,000 units of penicillin, 1,000 units in 0.05 c.c. of saline in ten different sites. These injections were repeated in approximately the same areas five days and ten days later, a total of thirty injections. One of these patients developed urticaria, dermatographia, lacrimation and conjunctival injection. In this case, as in all those in which the hypersensitive state had been induced by intradermal injection, the passive transfer test was negative.

*Case 1.*—Corporal C. P. H., twenty-nine years old, had been handling penicillin in the V.D. Clinic for six to eight months. Family and personal histories were negative for allergy. He first developed a scaling lesion on the left hand in July, 1944. This had cleared up entirely upon his return from a fourteen-day furlough. It again appeared on the left hand on resumption of penicillin handling and continued thus until December, 1944.

On December 15, 1944, intradermal skin test (100 units) and patch test were markedly positive. After this he continued working in the clinic but used a rubber glove on his left hand. On December 22, he developed generalized severe urticaria of arms, thighs and buttocks with angioneurotic edema of entire face (especially the eyes). This reaction continued for about seven days and did not clear entirely until January 3, 1945, thirteen days after the onset. The left hand still had a little scaling dermatitis. Routine intradermal tests in the allergy clinic were all negative.

Although he was taken off the job of handling penicillin, the left hand again developed a moderately severe dermatitis three days later, and this time he was hospitalized for twenty days. During this stay in the hospital a passive transfer was markedly positive. Nine months later the passive transfer test was negative but the intradermal skin test with 100 Oxford units of penicillin gave a tuberculin type of reaction two days after injection, similar to that described by Rotenberg and Welch.<sup>11</sup> Also the patch test showed a definite scaling five days after application of the patch.

*Case 2.*—Lt. J. H. M. gave a history of occasional mild bouts of hives in civilian life. He had a localized skin rash on both hands in 1943 while taking a sulfonamide for a draining left ear. The latter had been draining for several years off and on. From July 7, 1945, to July 22, 1945, he was given daily local applications of penicillin to this left ear canal. On August 6, penicillin intramuscularly (20,000 units every four hours) was started and continued until he had a total of 520,000 units. On August 7, 1945, sulfadiazine (Gm. 1.5 every four hours) was started but on the following day this was discontinued due to the appearance on the hands of a nodular itching eruption resembling the lesions that were present in 1943 on taking a sulfonamide. This present rash disappeared twenty-four hours after discontinuing the sulfadiazine. The penicillin was discontinued on August 11 with improvement noted in regards to ear drainage. Nine days after

## REACTIONS TO PENICILLIN—TRUITT

this drug was stopped the patient developed a severe and painful swelling of his knee, foot, ankle, and wrist joints with angioneurotic edema of face and eyes and generalized severe urticaria, the latter often iris-like in character. All of these lesions remained severe for approximately six days in spite of therapy and then subsided rather abruptly followed by exfoliation of both hands. He was then tested intradermally with 400 units penicillin with moderately positive results. The patch test was fleetingly positive (the hive lasting only twenty to thirty minutes). A passive transfer test was markedly positive. Eleven weeks later the intradermal and passive transfer tests were negative but the patch test was still positive, giving now a vesicular and later scaling lesion under the patch. The left ear was still draining slightly.

### DISCUSSION

While many writers on the use of penicillin (and certainly the literature put out by the manufacturers) skim lightly over the reactions to this drug, it can be seen from some reports, including the two cases cited in this paper, that these reactions can be quite severe. In the first place, in both of the cases it will be noted that previous contact (in Case 1 of long duration) was of definite importance as a sensitizing mechanism. It makes one wonder about the wisdom of the increasing widespread use of this valuable therapeutic agent in minor ailments for, if sensitization occurs, we may be denying its use to the patient in instances where it is specific and life saving. Secondly, the passive transfer and patch tests seem to be of value in proving the etiological factor where penicillin is concerned. This is in contrast to Rotenberg and Welch's findings where the passive transfer test was consistently negative. Thirdly, it will be noted that in Case 2 there was a gap of fourteen days between the first and second administrations of the penicillin. This brings to mind the danger of reaction incurred in the use of sulfonamides where a gap of over seven days is allowed to elapse between close courses of therapy. Lastly, after nine and approximately four months respectively, in the cases cited, patch and intradermal tests were still positive although the passive transfer had become negative.

### SUMMARY

Two cases of severe reaction to penicillin are added to the mounting series of untoward effects from this drug. Passive transfer, patch and intradermal skin tests seem to be of value in determining the etiology. Sensitivity can apparently remain, as determined by these tests for months after the reaction, indicating that caution should be taken if they are to be used again following a severe reaction.

### REFERENCES

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2. Binkley, G. W., and Brockmole, A.: Dermatitis from penicillin. Report of  
(Continued on Page 225)

# COMBINED PENICILLIN AND HYDROGEN PEROXIDE AEROSOL THERAPY IN LUNG INFECTIONS

## Preliminary Report

By HAROLD A. ABRAMSON, M.D., F.A.C.A.  
New York City

IT was previously shown by the writer<sup>2</sup> that by means of a simple commercial nebulizer (De Vilbiss No. 40), hydrogen peroxide solutions up to approximately 4 per cent (12 per cent urea peroxide in a 50 per cent glycerol solution) could be readily nebulized and remain fairly stable in the air of a small closed room. These hydrogen peroxide aerosols could be breathed in concentrations up to 3 per cent for short periods without much irritation. Both normal and allergic subjects could remain in a room filled with an atmosphere of these peroxide aerosols without discomfort. It was revealed that there were two important ways of using these aerosols in medicine:

1. As a germicidal aerosol similar to those studied by Twort and his group.<sup>14</sup>

2. Directly as an aerosol for local therapy in the lungs, similar to the use of epinephrine salt solution aerosol for the relief of bronchial obstruction and more analogous to the recent application of penicillin aerosol first published by Bryson, Sansome and Laskin.<sup>5</sup>

War activities of the writer prevented further exploration of the properties of these hydrogen peroxide aerosols until recently. It seems appropriate now to publish a preliminary report on progress made along the lines of therapeutic application. Bryson and Reese, under contract with the Technical Division, Chemical Warfare Service, at the Cold Spring Harbor Laboratory, will shortly publish data on the properties of germicidal hydrogen peroxide aerosols.<sup>4</sup>

### THERAPEUTIC AEROSOLS

Hydrogen peroxide, as a drug and antibiotic in aerosol therapy of the lungs and bronchi, might have therapeutic possibilities not possessed by penicillin which affects mainly Gram-positive organisms. Since streptomycin is not available<sup>6</sup> in large quantities, the exploration of the use of hydrogen peroxide as a general antibiotic agent for topical treatment of the lungs seemed desirable.

*Animal Experimentation.*—Mice were exposed to aerosols (particle radii:  $<2\mu$  containing 3 per cent hydrogen peroxide nebulized from a solution of 9 per cent urea peroxide) for two hours a day for seven days

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From the Biological Laboratory, Cold Spring Harbor, Long Island, New York.  
This investigation was aided in part by a grant from the Josiah Macy, Jr., Foundation, New York, and the Asthma Research Foundation, Boston.

The author is indebted to Dr. Vernon Bryson for his aid in the course of this study.

by means of De Vilbiss or Vaponephrin nebulizers operating between four and eight liters per minute. Except for minor irritation, twitching of the nose and huddling, there were no signs of the animal's being exposed to any unusual injury. As a matter of fact, an isotonic saline aerosol may produce the same symptoms. At the end of seven days, certain of the mice were sacrificed and compared with controls. There were no gross abnormalities in the lungs or in any of the other organs. The tissue sections have not as yet been studied.

*Human Tests (Normal Respiratory Tract).*—Before using peroxide aerosols on patients, volunteers breathed increasing quantities of urea peroxide aerosol. Both the De Vilbiss No. 40 and the Vaponephrin nebulizers were employed. The mist was delivered only during inspiration. No significant difference between the effects of the nebulizers was observed, as far as irritation of the upper respiratory tract was concerned. Following is an example of the type of experiment performed:

*Subject H.A.A.*—Nine per cent urea peroxide solution, plus 10 per cent glycerol dissolved in physiologic saline, was nebulized seventeen and a half minutes during the inspiration phase only. The De Vilbiss No. 40 was employed without rebreathing. The volume velocity of the compressed air used to generate the aerosol was approximately six liters per minute. The total peroxide solution nebulized was 2.1 c.c. Although this solution contained 3 per cent hydrogen peroxide, there was no irritation of the upper or lower respiratory tracts, nor did any symptoms occur twenty-four hours later.

Other similar experiments indicated that with certain precautions hydrogen peroxide aerosols could safely be used in man.

*Administration of Hydrogen Peroxide Aerosol in Clinical Conditions Technique.*—Either compressed air from a tank or from a compressor may be used. Oxygen in large tanks is convenient and in some ways preferable. The tanks should be equipped with a volume velocity gauge. The air flow should be regulated to the output desired and for the type of nebulizer employed. In general, between 4 and 8 liters per minute with the De Vilbiss No. 40 or the Vaponephrin nebulizer has been found suitable. The small stopper should be left in the vent opening. The reader is cautioned against directing the blast from the tip of the Vaponephrin nebulizer directly against the soft palate. The patient should be warned against placing the long tip of the Vaponephrin nebulizer all the way back in the mouth because the back of the throat or the soft palate acts as a baffle. This difficulty is not encountered in the use of the De Vilbiss No. 40 nebulizer which has a short tip.

The writer knows of no published scientific evidence which supports the point of view that rebreathing is essential. Indeed, since in rebreathing the patient breathes the directly nebulized mist only once every other

breath, the method of treatment becomes unduly prolonged. Olsen, who has published an extensive series of cases with excellent therapeutic results, applied the nebulizer directly to the mouth without other equipment, as advocated by Bryson and his co-workers.

A very simple cut-off can be obtained by merely boring or cutting a small hole about 5 millimeters in diameter in the tubing which connects the nebulizer to the oxygen tank. By this technique the usual glass Y tube is eliminated and the patient merely places his finger over the hole in the tube near the nebulizer (2 inches) at the beginning of each inspiration. It is important to stress to the patient that the early part of inspiration is most important for it is this phase which brings the air to the deep recesses of the lungs. In practice, the patient is coached with the word "in," indicating that the patient should breathe in, and "out," with the instructor making certain that the finger is placed on the cut-off just before the word "in" is used.

There is, of course, no reason, except economy, why a continuous generation of aerosol should not be employed. Although a continuous generation is wasteful of antibiotic material, it is insurance against faulty technique on the part of the patient. Masks also may be used to connect the patient directly with the nebulizer. Whether or not masks are desirable routinely must be determined by future quantitative experimental work. A careful study is that of Mutch and his co-workers. Their work will be reviewed elsewhere.

To summarize, then, all that is needed for penicillin aerosol therapy of the average ambulatory or hospitalized patient (or combined penicillin and hydrogen peroxide aerosol therapy of the lungs) is a source of compressed air or oxygen, a piece of rubber tubing and a suitable nebulizer. Rebreathing equipment is not required. Indeed, it is undesirable because of the prolonged therapy usually desired. The use of nasal tips for aerosol therapy of the lungs, plus rebreathing bag, is still open to question. How much penicillin is absorbed by the nasal mucosa and pharynx and how much is applied to those parts of the lungs where topical therapy is desired has not yet been published for equipment of this type. On the basis of the simplest type of aerodynamic reasoning, the less equipment between the nebulizer and the patient, the less turbulence will occur and the greater is the probability of the nebulized material being carried by convection into the lungs. It is this principle of *direct application of the aerosol to the rush of inspiratory air which is basic in aerosol therapy of the lungs*. It is this method which is recommended by the writer until suitable evidence to the contrary is provided by those advocating otherwise.

#### ILLUSTRATIVE CASE REPORTS

*Asthma: Allergic in Origin.*—A woman, aged fifty-four, who had asthma for twenty years and had periodic attacks of asthma complicated by very mild myocardial insufficiency was given hydrogen peroxide aerosol for ten minutes as

## AEROSOL THERAPY—ABRAMSON

9 per cent urea peroxide plus 10 per cent glycerol in physiological saline. The patient complained of very slight irritation, but in spite of the fact that 3 per cent hydrogen peroxide was administered, there was no cough, no irritation of the throat and no induction of an asthmatic attack.

*Asthma Complicated by Infectious Bronchitis.*—This patient, a woman, aged forty, was admitted two weeks before the initiation of hydrogen peroxide aerosol therapy to the hospital with respiration of 60 per minute, a temperature of 101 and a pulse of 120. X-ray study of the chest was essentially negative. During the following two weeks her asthma decreased considerably except for a sudden rise in temperature to 104 degrees which persisted only one day and disappeared after coughing up considerable mucus. The patient's general health and pulmonary condition improved. However, a persistent low-grade temperature, reaching 100.5, remained.

At this time the patient was given 1.3 per cent hydrogen peroxide as an aerosol plus 10 per cent glycerol solution in isotonic saline. This was administered for six hours per day for three days, ten minutes every hour. The total time that the patient received hydrogen peroxide aerosol was sixty minutes per day. A De Vilbiss No. 40 nebulizer was used. At the end of three days there was a slight irritation in the throat which, however, was relieved by washing the mouth and throat with physiological saline. The therapy was continued for four days. During this time the temperature gradually returned to normal. However, when peroxide was withdrawn, the low-grade temperature recurred. Immunological tests for brucellosis, typhoid, paratyphoid and infectious mononucleosis were negative. It is impossible to state whether the peroxide was responsible for the reduction in the patient's temperature. After thirty-one days of hospitalization, the patient returned home. Three weeks after reaching home her low-grade fever occasionally recurred and there was some exudative bronchitis. This patient was subsequently treated with combined therapy of penicillin aerosol alternately with urea hydrogen peroxide aerosol, shifting the antibiotics every two days. The routine advocated by Olsen<sup>11</sup> was employed for penicillin. The patient received 5000 units of penicillin as an aerosol every ten minutes for ten hours a day so that the lungs were exposed to five hours of penicillin aerosol per day. Penicillin was administered for two days, then withdrawn, and hydrogen peroxide aerosol, as 3 per cent urea peroxide plus 10 per cent glycerol dissolved in physiological saline, followed ten minutes every hour for seven hours per day. After two weeks of therapy, there was a marked decrease in bronchial exudate. The asthma persisted but was decreased in severity.

*Bronchiectasis (Suppurative).*—Combined therapy of penicillin and hydrogen peroxide aerosols, as indicated in the foregoing, with some modification is being employed by the writer in suppurative bronchiectasis. In the cases studied thus far, because of the dominance of Gram-positive organisms, the penicillin aerosol is continued three to seven days with hydrogen peroxide aerosol (urea peroxide 3 per cent plus 10 per cent glycerol in physiological saline) subsequently administered for two to three days. It may be recalled that the presence of glycerol diminishes the throat irritation, makes the peroxide aerosol more palatable and stabilizes the mist. I am indebted to Drs. George Baehr and Arthur S. Touroff for the courtesy of treating the following case which has come to operation:

This was the case of an obese woman, aged thirty-nine, with a fourteen-year history of intercurrent suppurative pulmonary disease. Physical examination, as well

## AEROSOL THERAPY—ABRAMSON

as x-ray report and laboratory data, revealed suppurative bronchiectasis with cavitation of the right middle lobe. About 50 c.c. per day of odoriferous purulent material were expectorated. Penicillin aerosol was begun on March 2, 1946. Penicillin was then discontinued on March 6 and urea peroxide aerosol was administered for two days. On March 8, penicillin aerosol was resumed. On March 14, pus was still present on bronchoscopy. On March 18, penicillin aerosol was applied until March 21 when penicillin was instilled directly into the cavity of the right middle lobe by Dr. Bender, as advocated by Siltzbach.<sup>13</sup> Similar instillations were made daily through the bronchoscope up to March 26. Approximately 100,000 units per day in 4 c.c. of saline were administered. On March 30, because of the rapid improvement of the patient since the beginning of combined penicillin aerosol, hydrogen peroxide aerosol and direct installation therapy, the patient was deemed ready for operation, and right middle lobe lobectomy was performed by Dr. Touroff.

Following are the findings and procedure of Dr. Touroff:

A right-sided submammary incision was made and the 4th rib exposed from the region of the sternum well into the axilla. The costal cartilage was divided close to the sternum and the thorax entered through the 4th intercostal space. Extensive adhesions were found between the involved middle lobe and the adjacent upper and lower lobes and between the lobe and the chest wall. After dividing numerous broad adhesions, the middle lobe was exposed. It was completely airless and was markedly shrunken in size. It was bluish red in color and quite indurated. It measured roughly 3 x 3 x 4. By blunt dissection, the middle lobe was separated from the adjacent lower lobe and the pericardium. Numerous vascularized adhesions were divided and the bleeding points ligated. The fissure between the upper and middle lobes was incomplete, so that in order to free the middle lobe, it was necessary to divide the pulmonary tissue of the adjacent portion of the upper lobe. After the latter had been accomplished, the defect in the upper lobe was closed with a series of mattress sutures of catgut. A typical dissection lobectomy of the middle lobe was performed. The hilar structures were closed with fine mattress sutures of chromic catgut and the stump was buried by uniting the remaining small amount of pulmonary tissue at the hilus over it with interrupted mattress sutures. On inflating the lung with positive pressure the upper and lower lobes almost completely filled the dead space which was left by removal of the middle lobe. 200,000 units of penicillin were instilled in the fifth intercostal space anteriorly. At the conclusion of operation patient was bronchoscoped on the operating table and only a small amount of dried blood was noted in the lower branches of the bronchial tree, on both sides. Patient left the operating room in good condition.

It should be noted that according to Dr. Touroff, the lung was "dry" on operation. A similar opinion was expressed by the pathologist who reported "chronic pneumonitis and bronchiectasis."

*Tuberculosis.*—Combined penicillin and hydrogen peroxide aerosol therapy is being used to study the effect on both the primary and the secondary infection in pulmonary tuberculosis. These clinical trials, together with animal experimentation, will be reported in detail in future communications.

## DISCUSSION

The case histories described in the foregoing are merely representative of the type of therapy now being investigated by the writer. No conclusions can be drawn as yet as to the efficacy of combined penicillin and hydrogen peroxide aerosol therapy as described in the foregoing. It is un-

fortunate that penicillin is destroyed by many oxidizing agents because, if this were not so, both penicillin and hydrogen peroxide could be nebulized simultaneously and both antibiotics applied topically to the lungs at the same time. In this way, the synergistic action of each on the other might have provided markedly enhanced germicidal activities.

Since it appears that penicillin remains in the lung tissues for some time, the possibility of synergism is not ruled out by our method of therapy. It is quite possible that exceedingly small amounts of penicillin retained by organisms might render them more susceptible to the action of peroxide. And, vice versa, organisms exposed to small amounts of peroxide might be rendered more susceptible to penicillin. Indeed, the interplay of germicidal activity of antibiotics of this type furnishes a complicated but hopeful approach to the therapy of bacterial and virus infections of the lung.

That the use of peroxides may be of greater importance in the therapy of infections other than hitherto believed has been recently emphasized by the paper of Keilin and Hartree.<sup>9</sup>

Keilin and Hartree point out that the function of catalase within the cell may not merely be protective. Their idea is supported by the fact that (a)  $H_2O_2$ , formed in a primary oxidation reaction, may oxidize hemoglobin within mammalian red blood cells, even though excess catalase is present; (b) a very small concentration of  $H_2O_2$  (one in four million) is toxic to various micro-organisms, even though catalase is present within the cells.

The presence of catalase within cells, therefore, does not constitute a definitive block to the antibiotic activity of  $H_2O_2$ . The possibility exists, however, that anticatalase may accelerate the reaction velocity in which  $H_2O_2$  acts as an antiseptic. The search for anticatalase will be part of our aerosol therapy program.

Another interesting aspect of the potential application of  $H_2O_2$  aerosol is that  $H_2O_2$  at body temperature has a significant vapor pressure. In other words, when an  $H_2O_2$  aerosol is inspired,  $H_2O_2$  gas exists within the lungs and it should diffuse very rapidly, indeed, to points inaccessible to larger liquid masses. It is conceivable that  $H_2O_2$  gas itself may be used for the therapy of lung infections.

The argument has frequently been raised to the writer that it did not seem likely that aerosol droplets could get to the interior of most pathological lesions in the lung. It is certainly true that when a mechanical block exists ordinary particles cannot get past a block. However, topical therapy of the lung is designed for several purposes: (a) protecting normal lung tissue from spread of infection, (b) walling off the infected areas already existing and, finally, if possible, (c) bringing the germicidal aerosol or gas directly to the site of the bacterium or virus producing the disease to destroy primary and secondary invaders of the living tissues. That this concept has been justified is well brought out by the successful results achieved in aerosol therapy of the lungs and bronchi.

## AEROSOL THERAPY—ABRAMSON

### SUMMARY

1. Hydrogen peroxide solution, plus 10 per cent glycerol in physiological saline, may be readily nebulized without loss of stability, whether used as hydrogen peroxide directly or as urea peroxide.

2. These solutions may be administered to both animals and man in germicidal concentrations without appreciable irritation.

3. Preliminary data on animals indicate that even when hydrogen peroxide aerosols of the type described are administered over prolonged periods, neither the lungs nor the eyes are damaged.

4. A brief report is made on the effect of administering hydrogen peroxide (urea peroxide) aerosols in cases of asthma, asthma complicated by infectious bronchitis and bronchiectasis with lung abscess. In these cases, not only was hydrogen peroxide (urea peroxide) aerosol used alone, but it was also combined alternately with penicillin aerosol. The use of combined penicillin and hydrogen peroxide aerosols provides a method of approach to the destruction of both Gram-positive and Gram-negative organisms with readily available antibiotic material.

5. A program is outlined in which combined penicillin and urea peroxide aerosol therapy, as described in the foregoing, is being applied to retard primary and secondary infections in pulmonary tuberculosis.

### ADDENDUM

Since the preceding paper was submitted for publication, the undersigned would like to report on progress made in the effect found on both primary and secondary infections in pulmonary tuberculosis during the past month by the use of penicillin and hydrogen peroxide aerosol therapy, applied as described in the preceding paper.

Two typical chronic advanced cases whose pulmonary lesions had remained stationary for months without material clinical symptoms, except irritating paroxysmal cough and positive sputum, have been treated for one month.

*Case 1, with laryngeal involvement:*

(a) The laryngeal pain was relieved by penicillin aerosol almost immediately.

(b) The cough has improved, being less forceful and not distressing to the patient.

(c) The purulent character of the sputum has decreased, with a decrease in viscous quality.

(d) Gram-positive organisms have disappeared from the sputum on culture. A Gram-negative bacillus remains on culture.

(e) The hydrogen peroxide aerosol does not increase the cough even though slight irritation of the back of the throat may occur after two days' use.

(f) Penicillin controls the usual cough although it is not certain whether this is due to the penicillin or the liquid contained in the aerosol.

(g) X-rays of the chest disclose no material difference.

(h) Sedimentation time essentially unchanged.

(i) Penicillin excretion—On the basis of occasional assays obtained thus far, at least 3,000 units of penicillin have been excreted per day. Levels up to 1.2 units of penicillin per c.c. of a twenty-four hour urine specimen have been found. This would make the twenty-four hour excretion over 3,000 units.

## AEROSOL THERAPY—ABRAMSON

- (j) Tubercle bacilli are still present in the sputum on smear and culture.
- (k) There has been a material improvement in the previously severe cough.

### Case 2:

- (a) The cough has improved as in Case 1.
- (b) The purulent character of the sputum has decreased as in Case 1.
- (c) Gram-positive organisms have disappeared from the sputum on culture smears of the sputum. A Gram-negative bacillus remains on culture.
- (d) The hydrogen peroxide aerosol does not cause irritation by increase of cough.
- (e) X-rays of the chest are essentially unchanged.
- (f) Sedimentation time essentially unchanged.
- (g) Tubercle bacilli are present in the sputum on smear and culture.

To summarize, two typical chronic advanced adult cases of tuberculosis have been treated for one month by alternating penicillin and hydrogen peroxide aerosol therapy of the lungs. Although the sputum of both has remained positive for tubercle bacilli, most of the other organisms have disappeared on culture and there has been a material decrease in the severity of the cough.

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## HYDATID ALLERGY

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**M**OST patients with an *Echinococcus granulosus* cyst (hydatid cyst) give a positive allergic reaction when injected intracutaneously with the fluid of cysts. This reaction was described and used as a diagnostic method by Casoni<sup>6</sup>, who injected 0.50 ml. of hydatid fluid intracutaneously in the forearm and observed the reaction produced twelve to twenty-four hours later. At the present time, only 0.10 ml. of hydatid fluid is injected in the skin.

Casoni's reaction is characterized by an erythema and swelling due to edema and to infiltration of the skin with eosinophiles.

Aside from the Casoni or delayed reaction, the injection of hydatid fluid can produce an early histamine-like reaction in patients with hydatid cyst, which was described by Pontano.<sup>48</sup> This early reaction generally appears from five to fifteen minutes after the intradermal injection of 0.10 ml. of fluid and is found positive in 90 per cent of patients with hydatid disease.<sup>14,33,34,35,37</sup> The Casoni or delayed test is found positive in a smaller percentage of cases. When a rupture of the cyst occurs or a suppurative process develops in the cyst in general, a positive delayed reaction is not found, but there is an early skin reaction, and a very definite positive fixation of complement occurs in the serum.<sup>16,37</sup>

Early positive reactions to hydatid fluid may be present in patients without hydatid cysts, but who have asthma, icterus, urticaria, dermatographism<sup>15,37</sup>, and liver carcinoma<sup>39</sup>, and in patients with other parasitic diseases, especially *Tacnia saginata* and *Taenia solium*.<sup>8,41</sup> In accord with my experience, a delayed positive reaction is present only in patients with hydatid cysts.<sup>25</sup>

Generally a positive skin reaction to hydatid fluid becomes negative two months after the extirpation of the cyst, but in some cases, a positive reaction may persist for several years after its removal.<sup>45,57</sup> The greatest percentage of positive skin reactions is found when the hydatid cyst is located in the liver or in the lung; negative reactions are very often found when the cyst is located in the brain or in the bones.

The skin reaction in hydatid disease is due to a reaction between the antigenic substances present in hydatid fluid and the reagents fixed in the skin cells. The serum of some patients with hydatid disease is found able to transfer the hydatid sensitiveness to normal individuals.<sup>49</sup> In accord with my investigations, while hydatid fluid can produce positive skin reactions in many patients, these reactions are not often transferable by the Prausnitz-Küstner technique.<sup>25</sup>

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## HYDATID ALLERGY—GRANA

### THE ANTIGENIC SUBSTANCES OF HYDATID FLUID

In the investigation of skin tests, the fluid of cysts of *Echinococcus granulosus* from four sources may be used: sheep, calf, pig and human being. After sterilization by Seitz filtration, phenol or merthiolate is added to the fluid as a preservative. It is recommended pooled samples from several sources be used and a clinical control be run in order to be sure of the antigenic power of the liquid.<sup>17</sup> Two antigenic substances have been obtained from the hydatid fluid: a protein by adding 5 per cent trichloroacetic acid<sup>11</sup> and a polysaccharide by adding alcohol to a 50 per cent concentration final to the deproteinized fluid.<sup>47,54</sup> These two antigenic substances can be obtained also from the membrane of the cysts.<sup>46</sup> The protein is the best antigenic substance in the ability to produce skin reactions, while the polysaccharide is a poor antigen.<sup>46</sup> The ability of hydatid fluid to produce skin reactions is not altered by heating to 95° C.<sup>36</sup>

### EOSINOPHILES IN THE BLOOD

In this parasitic disease an increase of the blood eosinophiles is often found. This increase may be as high as 25 per cent, and the eosinophiles return to the normal amount after the extirpation of the cyst.<sup>52</sup> When patients with hydatid cysts are injected intradermally with hydatid fluid, a great increase of eosinophiles in the blood is observed twenty-four to forty-eight hours later, which is of diagnostic significance because it is not produced in persons without hydatid cysts.<sup>1,3,4,5</sup> This particular reaction also can be observed in patients after the extirpation of the hydatid cyst.<sup>1</sup> An infiltration of eosinophiles is produced at the point of a positive skin reaction.<sup>3,56</sup>

I have confirmed all these observations<sup>22,23</sup>, and I have given particular diagnostic significance to the increase of eosinophiles, because no increase is produced in patients without hydatid cysts, in spite of injections of very large amounts of hydatid fluid. Unfortunately, in many patients with hydatid disease this eosinophilic reaction is not produced after the injection of hydatid fluid.

### REACTION OF GHEDINI-WEINBERG

Ghedini<sup>18</sup> and later others<sup>32,58,59,60</sup> showed that the serum of patients with hydatid cysts gives a positive reaction of fixation of complement using hydatid fluid as the antigen.

When a rupture of the cyst or a suppurative process is developed inside of the cyst, the reaction of Ghedini-Weinberg becomes intensely positive.<sup>16</sup> In some patients with a negative complement fixation and a positive intradermal reaction, the first reaction becomes positive twenty-four hours after the intradermal<sup>39</sup> or subcutaneous<sup>1</sup> injection of small amounts of hydatid fluid. This particular anamnestic reaction has been found by me in three of six cases<sup>22,23</sup> studied in these conditions.

## HYDATID ALLERGY—GRANÁ

### HETEROPHILE ANTIBODIES IN HYDATID DISEASE

An increase in antibody content in human sera against sheep erythrocytes has repeatedly been observed in pathological conditions. Thus, Hanganutziu<sup>31</sup>, in examining the blood of individuals receiving horse serum parenterally, found agglutinins, not only for sheep cells, but for those of horses, guinea pigs, calves and pigs. This occurs independent of the serum-sickness that may be produced in these individuals. Deicher<sup>10</sup> and Davidsohn<sup>9</sup> stated that these antibodies attain highest concentration in patients with serum sickness. Schiff<sup>33</sup> established that these heterophile antibodies appear also in serum-sickness produced after the injection of therapeutic rabbit serum. Increase in the titre of heterophile antibodies has been found in the serum with infectious mononucleosis<sup>44</sup>, in the serum of allergic patients<sup>55</sup> and in some patients who have received injections of liver extracts.

I have found<sup>20,21</sup> that a marked increase of agglutinins and hemolysins against sheep erythrocytes follows the repeated injections of hydatid fluid in some subjects with hydatid cysts. An increase of agglutinins for red cells of other animals, as well as for human red cells, types A and B, can be observed in certain patients who react most intensely to the intracutaneous injection of the hydatid fluid and are not observed in subjects with negative intradermal reaction, in subjects without hydatid cysts or in non-infected rabbits. I presented the hypothesis that for the appearance of this type of heterophilic antibodies previous sensitization of the tissues to the hydatid antigen is necessary. On the other hand, I found that an increase of similar heterophilic antibodies and eosinophiles<sup>26</sup> is produced in patients with positive skin reactions to *Ascaris lumbricoides* suum when these patients are repeatedly injected by the intradermal route with a saline extract of this parasite. The injections of the same parasitic extract in persons with negative ascaris skin reactions or in rabbits do not produce an increase of heterophile antibodies.

In summary, in some patients with positive skin reactions to hydatid fluid, a triple reaction can appear after repeated injections of this antigen: (a) hematological increase of blood eosinophiles, (b) heterophile serological reaction, increase of agglutinins and hemolysins against sheep red cells, (c) a rapid appearance of specific complement fixation antibodies. Unfortunately, the three reactions are not regularly produced, and, therefore, have a very limited diagnostic value.

### CLINICAL HYDATID ALLERGY

Typical crises of asthma due to the presence of a hydatid cyst in the liver or in the lung have repeatedly been observed.<sup>2,10</sup> Urticaria, angioneurotic edema and gall-bladder colics are sometimes present in patients who harbor hydatid cysts in the liver. Its possible allergic origin is shown by the beneficial effects of the extirpation of the cyst or desensitization with hydatid fluid.<sup>20,24</sup> In some of these patients we found an increase in

blood histamine<sup>28</sup>, but in most patients with hydatid cyst, blood histamine is normal or sometimes subnormal. In man, accidents produced by the rupture of hydatid cysts have been reported in several instances.<sup>13,38</sup> In general, all the symptoms described for human anaphylactic shock are reproduced: deep fall of blood pressure, tachycardia, nausea, vomiting, diarrhea, angioneurotic edema, giant urticaria, et cetera.<sup>7,13</sup> These symptoms are usually attributed to the phenomena of sensitization to foreign antigens present in hydatid cysts. The rupture of the cysts would bring the system into contact with massive doses of substances, to which the organism had been progressively sensitized and anaphylactic accidents would follow combinations of the antigens with the respective antibodies. This hypothesis, however, might be advantageously enlarged in consideration of the fact that severe to fatal shock develops among normal dogs after a first injection of hydatid fluid. This fluid appears to contain an anaphylactoid substance which is primarily toxic for dogs as shown by previous investigators and confirmed by us.<sup>29,50</sup>

#### ANAPHYLAXIS-LIKE REACTIONS PRODUCED IN DOGS BY HYDATID FLUID

The toxicity of the fluid of *Echinococcus granulosus* cysts has been reported repeatedly.<sup>12,19,42,43</sup> In the dog, the symptoms were somewhat similar to those of anaphylactic shock, since there was a fall of arterial blood pressure, leukopenia and incoagulability of the blood. After a first response the dogs become desensitized to further injections of the same substance (tachyphylaxis). I have shown first in collaboration with Recarte and Balea<sup>29</sup> and later with Rocha e Silva<sup>50</sup> that in some of the dogs injected with hydatid fluid there is an increase of the histamine content of the blood, but there is not a parallel relation between the concentration of histamine in the blood and the degree of fall of blood pressure. In some dogs there was a decrease, in some an early increase, and in others a late increase of the concentration of histamine in the blood. From these investigations, the general conclusion was drawn that histamine apparently is not concerned with this type of shock. The same type of shock but more grave is produced by the first injection of extract of *Ascaris lumbricoides* suum in dogs.<sup>51</sup>

In spite of Parisot and Simonin's findings<sup>42,43</sup> that the fresh hydatid fluid is highly toxic for the rabbit, we found that the purified products which are toxic for dogs do not produce symptoms in rabbits.<sup>30</sup> The injection of hydatid fluid produces a striking decrease of histamine in the rabbit blood at the same time that a drastic reduction of platelets is observed. From these experiments, the conclusion was drawn that histamine is more likely to be carried by platelets than by leukocytes in the circulating blood of the rabbit.

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## ASTHMA DUE TO BEE SCENT

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IT is not uncommon for individuals to show varying degrees of hypersensitivity to insect bites, wing scales, bodies of insects, the injection of venom or the introduction of salivary secretions.<sup>2,3,4,5</sup>

According to Ellis and Ahrens<sup>1</sup> any reference to hypersensitiveness to air borne allergens of bee origin could not be found in the literature. They report two cases in which asthma was initiated when near bees or objects that had been in contact with bees. Skin tests were positive to pollens from hives, honey, whole bee, bee abdomen, thorax, head, and other parts of the bee, but found a negative reaction to bee wings.

The following case will, I believe, be of interest because it shows that a patient may be sensitive to the scent of the bee and this scent which is heavy may cling to various parts of the bee body components of the hive and to any substance in which it may come in contact and so cause asthma.

The idea of scent-producing organs in bees was proposed by Sladen (1901). Nasonoff first described these glands in 1883. Snodgrass<sup>6</sup> says that Sladen, pointing out that bees were not known to have a sense of hearing suggested that the "joyful hum" of bees around the hive served as a signal and guide to the other bees. He believed that the sound is merely incidental to a fanning of the wings made to drive the scent away from the body, and that, not the sound, but "the scent produced forms a means of communication between the members of a swarm or colony."

Snodgrass continues: "This view concerning the function of the glands of Nasonoff is now generally accepted, and has recently been much elaborated by von Frisch (1923), who includes the abdominal scent as one of the important elements in the 'speech' of bees. He observes that a bee gathering nectar from flowers or drinking sugar water from a dish set out in the apiary flies about the place with the end of the abdomen protruded, and also exposes the outlets of the scent glands while drinking. In this way she marks the position of the food source with her odor, and the other bees, told of its existence by the customary dance of the returning bee in the hive, are then able to find it for itself in the field."

The patient, S. O. H., male, aged forty-one, provincial apiarist, consulted me first in 1938 with a history of asthma when anywhere near bees or on opening a small container with even a few dead bees sent for examination.

He gave no history of any other personal or family allergy. He was immune to bee venom, on one occasion he had over 200 stings and the only symptom was drowsiness. To this might be added the fact that he developed immunity to venom early in his career. Here follows his essential history in this condition as written at that time by himself.

"I began working with bees about seventeen years ago and had no disagreeable symptoms of any kind until eight years ago. At that time, while working in large apiaries near Lethbridge, I noticed an almost unbearable itching under the chin, and later on, an itching in the corners of the eyes. This occurred during the first two weeks of September, then, the bee season being over, I gave no further thought to the matter. As soon as I left the yards and washed my face and hands the symptoms I speak of disappeared.

"The following year the same symptoms occurred during the latter part of August and continued until the end of the bee season. They were more pronounced and the itching, especially in the corners of the eyes, would be there for several hours after leaving the yards. Three years after my first symptoms occurred I had symptoms which I considered to be hay fever. The itching under the chin disappeared. The itching in the eyes became more intense and they continued to water—there were frequent discharges of a watery mucous from my nose. Again these symptoms appeared about two weeks earlier than they had in the previous year. At this time I also had some evidence of very slight sinus headaches, but not serious.

"About four years ago I began to have difficulty in getting my breath from June on, and found it difficult to sleep. Usually, I sat in a chair until around 12:00 or 1:00 o'clock after working in a large apiary and then slept very soundly until the morning. There was no change in the intensity of the symptoms—though they seemed to appear a little earlier each year until last spring.

"Last spring the symptoms of what I thought to be hay fever attacked me when I examined my first yard, watery mucous discharges from the nose were pronounced, and breathing was difficult in the yards. In previous years I had noticed no difficulty in breathing until I went to bed. The symptoms became more and more severe throughout the summer, though I was handling fewer colonies than usual—and a pronounced lassitude, which gradually increased to grave weakness, grew on me through the summer. By August, I found that I could not sleep and rarely took dinner at night. Usually, I went home to bed, propped myself up with four or five pillows and tried to rest. I suffered from nausea throughout the evening and found no relief until 2:00 or 3:00 o'clock in the morning, when vomiting occurred. I would then sleep. During August I had such pronounced pain in my left lung that I consulted a physician, thinking I had pleurisy. He told me that it was a textbook case of allergy and advised me to resign from my position as Provincial Apiarist and get away from bee-keeping entirely."

In view of his history, tests were made of all the common pollens which cause pollinosis in this region with negative results.

Extracts were made from the various parts of bees with a buffer solution and tests done by the intracutaneous method. Positive reactions to all parts including the wings were markedly positive. Passive transfer was successfully carried out. A small part of a bee's wing was placed in the external angle of one eye and in less than one minute the whole eye was injected; one wing placed in the nostril caused sneezing and lachrymation.

Since the wings of the bee are composed of almost pure chitin, extracts were made of the wings of other insects composed of chitin with no positive reactions.

The patient suggested that possibly the scent was responsible for the asthma. In order to find if this was so, the bee wings were washed well with acetone before making a new extract. The test was negative. Next the scent glands were dissected out and the contents of one gland was placed in buffer solution. The skin reaction was now a marked positive.

The scent from one gland was placed in a small vial of ether. Three other vials of ether were prepared. The patient was unaware which vial contained the scent. He was given two vials of ether to inhale in succession with no effect. The third vial which contained the scent when inhaled caused an attack of asthma within one minute. The condition was severe enough to require adrenalin to control it.

Since it seemed unlikely that the patient would be able to carry on his occupation with bees he was anxious to engage in entomology. To find if other insects would cause his asthma extracts of over one hundred of these related to the bees were prepared and intracutaneous tests were carried out.

## ASTHMA DUE TO BEE SCENT—JAMIESON

These included the Orthoptera, Hemiptera, Coleoptera, and Diptera particularly.

Delayed reactions to a few members of the Coleoptera or water beetles were obtained. As some members of this subfamily possess rectal glands which excrete volatile offensive gaseous or liquid substances, it is possible that these reactions were due to these and of an irritant nature.

### SUMMARY

A case is reported in which a patient suffered from asthma from the scent of the bee. He gave skin reactions to all members of the superfamily of the Apoidea, but to no other member of the superfamily of Hymenoptera. Asthma resulted from inhalation of bee scent glands dissolved in ether. Positive skin reactions were obtained from an extract of bee wings. Passive transfer was carried out. An extract of bee wings washed with acetone gave negative skin reactions.

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A METHOD OF OBSERVING TRANSIENT LEUKOPENIA. Essex, H. E., M.D., and Grana, A. (By invitation), Mayo Foundation, Rochester, Minnesota. *Federation Proceedings*, Part II, 5:25, February, 1946.

By means of a transparent chamber (Clark, Florey) inserted in the ears of rabbits, the authors observed the leukocytic behavior in newly formed blood vessels following intravenous injections of certain amounts of glycogen, gum acacia, extracts of *Ascaris Suum* and hydatid cyst fluid. These injections were followed by a majority of the leukocytes adhering to the walls of the veins in one or two minutes and ceasing to move. The leukocytes were observed to adhere to the vessel walls and to each other, forming small clumps. In 15 to 30 minutes the cells usually separated from each other and the vessel walls, and again entered the circulation. During that period of their vessel adherence, there was a consequently marked leukopenia in the blood obtained from the ear or leg vein. The lowest leukocyte counts corresponded with the period of altered behavior when the cells were adherent to the walls of the veins.

Their observations suggest to the authors that the reaction is a general one. They also noted that the behavior of the leukocytes was not influenced by injections of glucose or a serum or physiologic salt solution.

The authors are continuing their observations by noticing the behavior of the leukocytes following the injection of other substances as well as that following anaphylactic shock, in order to determine whether a chronic leukopenia can be produced by the prolonged administration of certain substances.

## HEADACHES

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**M**IGRAINE has been defined as paroxysmal attacks of hemicrania (occasionally bilateral headaches), which are associated with sensory and motor disturbances. These latter disorders, effecting vasomotor changes, crossed hemicrania, hemianopsia, unilateral paresthesias, and the like, point toward an involvement of the cerebral cortex itself.<sup>1</sup>

Migraine is commonly considered a one-sided headache usually with an aura, with nausea and vomiting, vertigo, lethargy, frequent photophobia, and terminating in a relief as sudden and unexplained as its onset. In this present study, migrainous headaches with one or more of the usual prodromata were found to be unilateral, generalized, and, in 3 per cent, unilateral and generalized on different occasions in the same individual. In an effort to include only migraine, the term *tension headaches* was used in this series until a definite link could be made between the unilateral and the more generalized headaches. Comparison later established them to be of the same etiological factor, the principal point of variance being their distribution.

Headaches associated with nasal blockage and obvious Horton's syndrome cases were excluded from this study. The auras that this group experienced varied from a sudden oppressive fatigue to olfactory, visual, and auditory ones. Eighty-seven per cent of the patients in this series at one or more times had received ergotamine tartrate at the onset of an attack not only for relief but also to serve as a further diagnostic aid.

In 1927 Vaughan demonstrated that food sensitivity could be responsible for migraine.<sup>13</sup> Others have confirmed this fact.<sup>5,12</sup>

This malady has also been studied extensively from the standpoint of endocrine involvement. Mazer and Israel conclude that some migraine is caused by an allergy to the follicle-stimulating hormone which could be suppressed by adequate estrogen therapy. They failed to give relief by estrogen therapy in only five out of thirty-four patients designated as "the menstrual type."<sup>9</sup> Another opinion describes an imbalance in the anterior pituitary-ovarian relationship with hyperfunction of the pituitary and hypofunction of the ovaries in migraine production.<sup>11</sup> Hoffman cites Goldzieher's opinion by explaining migraine as an outcome of increased water and salt retention in the tissues preceding menstruation. Adding to this an increased nervous instability and an increased capillary permeability which normally precede menstruation, there is an increase in intracranial pressure resulting in pain. The increased intracranial pressure was thought to stimulate anterior hypophyseal function causing an elaboration of more gonadotrophic hormone.<sup>7</sup>

Psychologically the migraine sufferer has been described as one socially and emotionally maladjusted, with psychoneurotic, but not psychotic,

trends in the personality.<sup>10</sup> The possibility of a disturbed sympathetic innervation with resulting vasomotor changes has also been suggested in regard to production of migraine.<sup>15</sup> Shyness, rigidity of personality, perfectionism, extreme sensitiveness, sex maladjustment, abnormal attachment to a parent, emotional tension, anxiety, driving ambition, and other factors have been offered as the psychobiologic aspect of migraine sufferers.<sup>16</sup>

It would seem that the main factors to be considered in the proper evaluation of the mechanism producing migraine as well as its treatment are allergic, endocrinological, and psychic in nature. The common denominator of migraine or tension headaches is a cerebral edema produced by a primary vasomotor spasm followed by a secondary vascular dilatation.<sup>8</sup> Increased intracranial pressure has been reported to be present during the attack and is eventually equalized with its termination.<sup>6</sup> The variety and difference in pain distribution, as well as aura experienced, can be explained on the basis of the part of the brain involved and whether the edema be localized or generalized<sup>2,4,14</sup>; and also by distention of the cranial arteries involved.<sup>3</sup>

In this series of one hundred migraine or tension headaches, sixty-three were female and thirty-seven male. Each was studied from the allergic, glandular, and physiological viewpoints. Consultations with gynecologists, endocrinologists, psychiatrists, neurologists, and allergists were obtained in all doubtful cases.

The emotional factor embodied the psychoneurotic pattern and at no time was a frankly psychotic or mentally defective individual uncovered.

Diagnoses of glandular deficiencies were made after careful history, physical examination, laboratory, x-ray, smear and tissue studies had been done. Only one case, and that of a male, showed a glandular (gonadal) hyperfunction.

The allergic familial history was considered contributory if migraine, "sick, one-sided headaches," bronchial asthma, hay fever, or eczema were found to have existed. If, in addition to migraine, the patients had one or more allergic conditions such as hay fever, eczema, and the like, this was thought important enough to record in favor of an allergic factor.

The entire group was tested completely to foods and the gastro-intestinal factor was not considered salient unless at least ten or more strong (4+) reactions were obtained. Tests were made by scratch, then endermal methods. This was followed by endermal retesting. In some cases, diet elimination studies with carefully recorded food charts were required. In the earlier cases, leukopenic indices and blood enzymic studies were carried out but later omitted because of unreliable results obtained.

In order to clarify better the problem of physical allergy in those who complained of precipitation of headaches when exposed to drafts, the incidence of dust sensitivity was included along with the thermal factor.

# HEADACHES—CROWE

TABLE I. FACTORS IN REGARD TO HEADACHES

	Generalized (46)	Unilateral (51)	Entire Group (100)
1. Emotional	50%	59%	54%
2. Glandular Deficiencies			
(a) Pituitary	15%	19%	18%
(b) Thyroid	34.7%	35%	35%
(c) Gonadal	39%	49%	38%
3. Hypergonadal	2.1%	0%	1%
4. With Allergic Familial History	39%	36%	36%
5. With Concomitant Allergy	43%	46%	46%
6. With Food Allergy	63%	82%	73%
7. With Inhalant Allergy	34.7%	56%	48%
8. With Thermal Allergy	36.9%	36%	38%
9. With Marked (4 +) Dust Allergy	28%	24%	26%
10. Type Headache			
(a) Right unilateral			22%
(b) Left unilateral			33%
(c) Total (left and right unilateral)			55%
(d) Generalized			46%
(e) Both			3%

Only marked (4+) dust sensitivities were included in this study.

Over half of the entire group had unilateral headache with a psychoneurotic predisposition, but the most important factor is the gastrointestinal allergic one. Next in importance to food and emotional factors comes inhalant allergy. That the allergic factor is the most important one is substantiated by the high incidence of the allergic hereditary factor and the presence of other allergic manifestations in the individual. The majority manifested sensitivity to temperature changes alone rather than to dust.

Gonadal and thyroid deficiencies were the prominent glandular abnormalities found. Pituitary deficiencies in this series proved practically negligible. Only one case of hypergonadism was seen.

Whether the headaches manifested were unilateral or generalized, the factors for the entire group remained fairly constant; however, in unilateral headache there was the greatest incidence of food allergy, emotional instability, and inhalant allergy in the order named (Table I).

The principal sensitivities to foods in the majority of cases were cereals (predominantly wheat), the legumes, seafoods, and cow's milk.

Treatment consisted of diet elimination, pollen desensitizations, gonadal substitution therapy, and thyroid when indicated. The patients, with the exception of two, were able to overcome their conflicts without aid of a psychiatrist.

All patients remained free of migraine so long as absolute avoidance of the offending foods was observed and so long as the emotional factor was controlled.

Thermal allergy was treated by contrast baths. The degree of favora-

ble response to this method alone cannot be ascertained, in that other desensitizations were being simultaneously employed.

Migraine, because of its predominant allergic basis, should be handled by the allergist, who must be constantly aware of the psychoneurotic element in over half of the migraine sufferers he sees. This important psychological aspect of the problem, along with indicated glandular therapy, and necessary allergic desensitization, offers the best chance of recovery.

The term "tension headaches" can be discarded. Enough common factors have been established, regardless of headache distribution, to warrant the entire series to be called migraine headaches.

Ten per cent of the patients have had recurrence of migraine while on treatment. In most cases the attack was traced to a dietary violation. A minority of this group of recurrent headaches precipitated the migraine by an emotional conflict.

## SUMMARY

1. Migraine, whether unilateral or generalized, is explained on a basis of localized or generalized cerebral edema with resulting increased intracranial pressure.

2. Listed in order of their importance are factors to be considered in the proper management of migraine sufferers: food sensitivity, the psychological aspect, inhalant sensitivity, physical allergy, and glandular deficiencies.

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## SEDIMENTATION RATE—A DIAGNOSTIC AID IN ALLERGY

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IN searching for additional aids in differential diagnosis of allergic and non-allergic diseases, a record was kept of 3,000 sedimentation rates in the past year. These readings covered many different diseases. An attempt has been made to use these readings in an effort, if possible, to avoid unnecessary allergy diagnostic procedures. These observations seem to explain part of our past failures, since it appears many symptoms were not due to allergic exacerbations.

The sedimentation tests were made with a Landau-Adams apparatus, and results were noted at the end of one hour. When possible, observations were made on each patient throughout the year. Frequent observations were made in seasonal cases during their seasonal increase of symptoms. Normal readings in this apparatus are included in the range from 1 to 10 mm. Infectious diseases have readings well above 25 mm.

Infections and other conditions causing an increase in sedimentation rates are:

1. Pharyngitis, adenoiditis, rhinitis, dental caries, rheumatic fever, endocarditis, chorea, nephritis, complicated tuberculosis, erythema nodosum, salpingitis and other gonorrheal infections, toxic malignancies, syphilis, tonsillitis, endometritis, chancroid, cholecystitis, rectal abscess.
2. Blood dyscrasias as leukemia, purpura, polycythemia vera, pernicious anemia, et cetera.
3. Pregnancy and tubal pregnancy.
4. After use of x-ray or radium therapy—gelatine.
5. Vascular lesions.

Conditions which inhibit the sedimentation rate are: jaundice (if the bile acid is increased in the blood), alcohol, novasural, sodium salicylate and quinine.

## RESULTS

1. *Allergic Migraine*.—Nine cases. All had readings between 2 and 8 mm. in one hour, except two. One had cholecystitis and colitis, and the

Suggestions or articles intended for this department should be submitted to Dr. L. O. Dutton, 616 Mills Building, El Paso, Texas.

## CLINICAL PATHOLOGY AND LABORATORY PROCEDURES

rate dropped from 40 to 10 mm. when these factors were eradicated. One had a reading of 17 mm. which went down to 10 mm. when her sinusitis subsided.

2. *Histaminic Cephalalgia*.—Three cases. All readings 3 to 4 mm. in one hour.

3. *Bronchial Asthma*.—Forty-five cases of uncomplicated bronchial asthma had readings between 3 and 10 mm.

4. *Hay Fever*.—Thirty-two cases. All had sedimentation readings between 1 and 10 mm. in one hour. Pollen in the air had no bearing on their readings.

5. *Allergic Rhinitis*.—Sixty-five cases. All had readings from 1 to 10 mm. when controlled under proper management. Ten cases had an increase above 10 mm. either before treatment started or at some time during the year because of other causes. The sedimentation rate returned to normal when infections were cleared.

6. *Hives*.—Six cases of uncomplicated and proven allergic hives had normal readings.

7. *Allergic Bronchitis*.—Nine patients. Seven had normal rates at the start. Two cases had 20 and 26 mm. These became normal as soon as the complicating infection was cleared.

8. *Angioneurotic Edema*.—Five cases of angioneurotic edema which were proven to be of allergic origin had readings from one to ten mm.

9. *Eczema*.—Fifteen cases of eczema had normal readings.

Of the complications that arose in allergic patients, some are listed with their effects on sedimentation rates:

Acute arthritis (two cases)—readings 25 to 45 mm.

Acute gonorrhea (one case)—reading 50 mm.

Influenzal bronchitis (twelve cases)—readings 30 to 45 mm.

Rheumatic fever (two cases)—readings 30 to 40 mm.

The mechanisms by which sedimentation rates are changed are:

- (a) Any condition causing an increase in viscosity of the blood causes an increase in sedimentation rate.
- (b) Decrease of the albumin in the blood causes an increase in sedimentation rate.
- (c) In a tuberculosis patient getting BCG vaccine, the sedimentation rates become normal when the patient develops allergy to the vaccine.
- (d) Destruction of tissue by x-ray or by tumors causes absorption of tissue or toxic substances with increased sedimentation rates.

## CONCLUSIONS

Sedimentation readings have been an aid in differentiating allergic and non-allergic diseases and have avoided some unnecessary allergic diagnostic procedures. They have also explained some of our failures. Many

former failures have been brought under control by aid of other medical therapy which explains some of the puzzling "flare-ups" in allergic patients. Sedimentation rate observations are done very easily and have a very small percentage of errors (5 per cent). These observations would indicate that routine blood sedimentation observations should be done on allergic patients, since many patients with hypersensitiveness have complicating diseases which are not of an allergic nature. This simple procedure may be a diagnostic aid when differentiating those allergic patients who are suffering from other diseases as well.

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*Correction.*—On Page 139 of the March-April issue of the ANNALS OF ALLERGY there was an error in the formula of the stain. The formula should read:

Eosin, yellowish, alcohol and water soluble	0.5 mg.
Ethyl alcohol	95%/100. c.c.

## PENICILLIN DERMATITIS BASED ON TUBERCULIN-TYPE SENSITIVITY

(Continued from Page 195)

injections produced a reaction. The latter was of the delayed so-called tuberculin type. All patch tests with penicillin on skin previously unaffected were negative. The clinical lesions as well as those produced experimentally on a finger of the patient presented the picture of a "dysidrotic" dermatitis. This case is considered as a penicillin dermatitis based on tuberculin-type sensitivity.

Two of four volunteers used as controls in passive transfer became allergically sensitized to penicillin.

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# Editorial

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## BACTERIAL ALLERGY

The allergist is used to dealing with non-viable and *per se* non-toxic antigens. Therefore, it is not surprising that he sometimes finds it difficult to adapt himself to the complications that necessarily arise if the *causa peccans* is viable and (sometimes) poisonous. It is obvious that an antigen that is viable and not indifferent *per se* must greatly complicate both the clinical picture and the considerations dominating its analysis. As a matter of fact, for what is commonly understood by the term "allergic diseases," there is so little clear-cut evidence of supersensitivity to micro-organisms that the clinician is greatly tempted to simplify his position by denying the existence of what cannot be reduced to simple facts.

Psychologically his attitude is quite understandable. However, a number of micro-organisms—and the term is used deliberately because it includes viruses as well as bacteria—are antigenic. For almost any of those which have been more closely investigated, antigenicity has been found for more than one component such as proteins, carbohydrates and lipids. And furthermore, it is a fact that the host may become supersensitive to such substances, a piece of knowledge put to use every time we make a tuberculin test. Thus, at least for tuberculosis, the occurrence of supersensitivity has become so trite that it is not often associated any more with the common ground on which our information both on tuberculin supersensitivity and on allergic diseases has grown.

Moreover, the physician knows of the accelerated reaction after repeated inoculations, say of vaccinia virus. He accepts the fact that scarlet fever represents a supersensitivity to a streptococcus that in itself is not very toxic. He has learned, even though he does not usually employ it, that an infection rather regularly leaves demonstrable signs of reactivity to microbial substances as, for instance, pneumococcal carbohydrate. Most of these phenomena do not fall neatly into the pattern we are accustomed to see in allergic diseases. But they all represent the basic phenomena of highly and occasionally catastrophically (tuberculin!) increased and accelerated reaction. Thus, it appears that the general practitioner may be able to give a point to his specialized colleague.

Of course, the allergist may reply that this is all perfectly true and correct, but that is none of his concern because he is not dealing with

infectious diseases. Thus, the question comes up whether he is or is not. The answer depends on what one calls infection. It is certainly "no," if the term is restricted to epidemic diseases. However, the outer and inner surfaces of the human body are covered with micro-organisms. Most of them are harmless enough commensals, others are conditionally pathogenic, as for instance, the flora of our throat, and occasionally there is a powerful killer which is just waiting for a port of entry. The allergist will agree that the integument of every human being is somewhere penetrated every day by micro-organisms which are immediately dealt with by the usual defense mechanisms without leaving any record worthy of medical attention. Still one should think that these contacts are bound to be intensive enough to impress the mechanism that leads to antibody response, and indeed we have evidence that that is the case. Also, there is the problem of intestinal absorption of bacterial antigens. (The counterpart for yeasts and molds is positively known, as for instance, in the cases that tolerate milk but not cheese).

It would be more natural to wonder why such continuous antigenic stimulus does not lead more frequently to striking and easily recognizable allergic reactions than to doubt that microbial sensitization does occur. One may make the conjecture that in continuous intermittent contact, immunity phenomena dominate the picture, just as we are often able to overcome pollen allergy by perennial immunization. From this point of view one may wonder whether the familiar disposition to trivial infections noted, for instance, by Locke and Coca may not be based on a disturbance of the normal balance between sensitization and immunity, in favor of the former in individuals particularly prone to allergic reaction and/or underendowed in their immunity apparatus.

In any case, there is no basic reason why persons of the necessary constitutional make-up should not react vehemently to bacterial antigens. In the case of certain types of asthma, this is quite widely and naïvely accepted to be the case. The scientifically minded among us will say: "quite possible but where is the proof?" Indeed, there is no proof. However, the point is that there is no proof not because there is nothing to be proved but because we really have made no systematic effort to prove or disprove. As to these things we are actually still in a position comparable to that in which we were at a time when people knew quite well they would get hay fever attacks when they went for a walk through a meadow, but nobody knew what that meadow did to those people to make them weep. The meadow contains many things, and it took some doing before we found which of the many things was the causative agent. Our inner and outer body surfaces harbor a great variety of micro-organisms and it will take some doing to find out whether, for instance, bacterial antigens may make an asthmatic wheeze—as conjectured—and, if so, in what cases and under what conditions. The

allergists started by asking the botanist what grows on that meadow, and then they put to use what they had learned. The allergists will have to go to the bacteriologist in order to find out about our microbial guests, and then they will have to apply what they have learned. For instance, they will learn to take into consideration the great variety of microbia involved and they will discover that it is not enough to know that a certain species is present. They may have to apply what the bacteriologist has found out about the immunological types of these species because that is what determines the immunity reactions and would therefore be expected to dominate the specificity of allergic reactions. To return once more to the example of the meadow: It obviously would have been wrong if the search for the agent causing hay fever had been restricted to poisonous plants. From what has been said before, it ought to be just as obvious that the investigation of the problem of the relations between microbial substances and allergy should not be restricted to pathogens and particularly to organisms of high pathogenicity. Commensals may be as important as the known pathogens.

It looks like a big order, and it is one. But only by putting to use the painstaking methods of modern bacteriology we will be able to replace notions by exact information. And this information will be necessary before we can state with any degree of confidence whether or not microbial antigens are involved in a given manifestation of allergy. Maybe a few years hence we shall be able to talk less about conjectures and more about facts.

A.J.W.

## REACTIONS TO PENICILLIN

*(Continued from Page 198)*

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# Progress in Allergy

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## THE HOUSE DUST ANTIGEN

### A Critical Review of the Literature

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THE present historical review lists the more important contributions to the problem of the house dust antigen and its relation to respiratory tract allergy. It was hoped that by reviewing the data published since Kern's first paper in 1921<sup>43</sup>, a more definite direction might be given to future experimental and clinical investigation in this field.

The material in each of the subsections has, in some measure, been arranged chronologically so that the development of our understanding might be followed. Of necessity, the earlier points of view, some of which were subsequently repudiated or corrected by the original authors or by others, had to be included as presented in their first published state. Some of these earlier views, although not at present tenable, may serve as a framework for further research. Others of these earlier views now considered true may, in the same way, prove to be otherwise; for instance, Cooke's postulation<sup>23</sup> regarding the specificity of the house dust antigen.

The last most extensive critical review of the subject was made by Walzer<sup>66</sup> in 1938.

The present review discusses, in order, the following aspects of the problem; the question of the specific antigenicity of house dust; its chemistry; its biological, chemical and clinical relationships to moulds, bacteria and other inhalants; the preparation, purification and standardization of the extracts both chemically and biologically; the diagnostic considerations; the therapeutic utility; and the objective evaluation of the clinical results.

In 1921, Kern<sup>43</sup> wrote, "The sensitivities to other dusts, as for example to the dust of dirty cotton mattresses, woolen rugs, and matings, are unique in that skin-testing for the specific type of material is negative," thus calling attention to a new inhalant factor in respiratory tract allergy. Cooke<sup>23</sup>, in 1922, demonstrated that house dust was a definite etiological factor in the production of bronchial asthma and at the same time assumed that individuals sensitive to dust did not necessarily show sensitivity to other substances used as testing materials. He felt that there was no agreement between dust extract sensitivity and sensitivity as demonstrated by other extracts. He concluded, therefore, that house dust contained an antigen peculiar to itself.

Spivack and Grove<sup>58</sup> reported in 1925 that in normal individuals the sites sensitized with the sera of house dust sensitive patients and subsequently exhausted with house dust extract nevertheless reacted positively to tests with other inhalants. The serum of a patient sensitive to both horse serum and to house dust was used for passive transfer site exhaustion experiments. Following exhaustion of the sites with horse serum, reactions to house dust were demonstrated as evidence of the specificity of the house dust antigen.

Van Leeuwen et al<sup>62</sup>, in the same year, attempted to correlate the dust allergen with mould activity by noting that *Aspergillus fumigatus*, acting upon new kapok, produced a new extract capable of producing positive skin reactions. Frugoni and

## PROGRESS IN ALLERGY

Ancona<sup>38</sup> are credited with an original observation in reference to the appearance of the dust antigen in aging feathers.

Grove and Coca<sup>39</sup> at this time reported that the removal of nitrogen from extracts of pollen, house dust, horse dander, and green peas by digestion and dialysis caused no reduction in skin activity for pollen and dust extracts but a marked reduction in the extracts of horse dander and green peas. They concluded that the atopens present in pollen extracts and in dust extract were not, or did not seem to be, of the usual protein character common to other extracts.

In 1926, Rackemann and King<sup>53</sup> advanced two theories for the causation of bronchial asthma. They considered that the prime factor in the first group of supposedly house dust sensitive patients was not the dust sensitivity which ordinarily causes no symptoms, but the presence of the respiratory infection which affected the portal of entry and allowed dust to become absorbed more readily. There was a second group of patients in whom bacteria alone were responsible, the patient responding with a true hypersensitivity to a substance native to the bacteria or occurring as a product of their metabolism. They felt that the skin reactions to house dust were relatively unimportant since extracts of house dust prepared by Coca's method, and injected intradermally, failed to cause reactions of the urticarial type. As a corroborative evidence they cited the absence of constitutional reactions and the disappointment which resulted from attempts to hyposensitize patients with house dust extract. They were unable, however, to furnish proof of bacterial hypersensitivity by the production of immediate, local reactions of the urticarial type.

In 1927, Rowe<sup>55</sup> reported that 45 per cent of his patients, suffering from bronchial asthma, demonstrated a positive skin test to house dust extract. In seventy patients sensitive to house dust, by skin test reaction, there were numerous reactions to other inhalant proteins of animal origin. The author felt, therefore, that "reactions to house dust might be due to dust arising from certain articles of furniture rather than from some unknown source," as had been suggested by Cooke. Rowe concluded, therefore, that the possibility of an unknown specific substance in house dust was unlikely.

Ramsdell and Walzer<sup>54</sup> reported in the same year that, as demonstrated by the Dale technique, they had been unable to sensitize guinea pigs with a dialyzed dust extract, and therefore concluded that dust extracts had little or no antigenic properties for this test animal. In 1934, however, Harrison<sup>41</sup> using an alum precipitated extract was able to sensitize guinea pigs to house dust extract much more successfully.

In 1929, Cohen<sup>15</sup> published data demonstrating that nineteen of two hundred patients, who gave large skin tests to dust made from their mattresses, although they did not react to cotton or kapok, achieved complete relief when the offending article of furniture was eliminated. Recurrences could be prevented when mattresses were covered with impervious materials. At this time, Cohen considered moulds to be responsible for the change in the antigenic qualities of the mattress. In a later communication, in 1935, Cohen, Nelson, and Reinartz<sup>21</sup> eliminated moulds as a factor in house dust sensitivity. Five patients who gave positive skin tests to house dust only were tested with extracts of moulds obtained from the samples of dust to which they were sensitive, with none reacting. In the collection of house dust for the testing of such patients, samples from rugs and draperies which might contain many contaminants were avoided and the dust taken from bedding and overstuffed furniture was preferred. It was observed that an allergen developed in cotton linters as a result of aging, and that passive transfer experiments proved an identity of dust extract and linters extract, since either would neutralize the reagins for the other in a dust sensitive serum injected into a normal skin. It was also possible to demonstrate the fact that the protein responsible for cottonseed sensitivity differed

from that developed in aging cotton linters. Fresh cotton linters failed to give positive reactions in ten dust sensitive patients, but the same linters, aged in various ways, gave positive skin tests. The evidence suggested that house dust antigen was a degenerative product of cotton linters.

Walzer<sup>66</sup>, discussing the experiments of Cohen and his colleagues, noted that they had not proven that the degenerative product of cotton linters (or of kapok or feathers) was a combination of degenerative products which made up house dust, or whether it was a single end-product of all such substances. He further criticized their work on the basis that dust reagins were not demonstrated in his ten subjects who, negative to fresh cotton linters, proved positive to extracts made from aged linters. He noted also that no report had been made of the degree of positive skin reactions with this extract in normal control subjects.

Cazort<sup>12</sup> then compared linter extracts made under varying conditions of light, heat, moisture and contamination with antigenic dust. He found positive skin tests to be present with these extracts in all of the patients sensitive to house dust extract and, again, was unable to prove the presence of any antigenic properties in extracts made from fresh cotton linters. In answer to Walzer's criticism of the work of Cohen and his colleagues, Cazort showed that the serums of dust sensitive patients used for passive transfer experiments reacted to extracts of old cotton linters, but not to the extract of new linters.

Wagner and Rackemann<sup>63</sup>, having noted that Cooke in his original work on house dust had failed to consider kapok as a common allergen, made a number of studies concerned with this substance. They discovered that many of their asthmatic patients gave positive skin tests to extracts of old kapok fibre, and that the removal of the offending mattresses, pillows, and stuffed furniture afforded relief. Dusts taken from kapok produced large skin reactions in nine of ten asthmatic patients. Tests with the extract of the kapok fibre, the seed, and the hull proved the active ingredient to be contained in the fibre. It was presumably on the surface, freely soluble, and readily removable. Dialysis with cellophane removed the greater part of the active principle. The extract was not changed by boiling, but the active principle could be adsorbed on charcoal, and gave a positive Molisch and a negative Biuret test. Their work suggested that the activity of kapok was not a function either of the nitrogen factor or of the total solid content and that the nitrogen so obtained was not wholly protein in nature. In addition to other qualities, the extract could not be used successfully to sensitize guinea pigs.

Further studies with skin tests demonstrated that, of five normal subjects, two gave positive reactions. Walzer<sup>66</sup> suggested that these two positive reactions were due to the irritative properties of the extract and as a further indication that these reactions might be irritative, cited a group of thirty-eight supposedly kapok dust sensitive patients, in only ten of whom reagins were found to be present.

At this time, the mould theory of the origin of dust as advanced by van Leeuwen<sup>62</sup> was reconsidered by Feinberg<sup>35</sup> who reported that half of his dust sensitive patients reacted to fungi, while Brown<sup>9</sup> stated that skin tests to their own dust gave positive reactions in dust sensitive patients, although they often reacted negatively to dust derived from other sources. Although scratch tests made with extracts of moulds obtained from mattresses or house dust failed to give positive reactions, there were immediate urticarial reactions when tests were performed with the original mattress and dust extracts. The author nevertheless felt that moulds were important factors in the symptoms in dust sensitive patients, although he was unable to prove the presence of an allergenic substance produced by the action of moulds or bacteria upon dust. Lamson and Rogers<sup>44</sup> were also unable to substantiate the theory that mould sensitivity was a determining factor in the cause of house dust reactions.

Rackemann<sup>22</sup> returned to his earlier work with kapok, in order to determine what

part, if any, was played by moulds in the phenomenon of dust sensitivity. Since old and new kapok reacted so differently both chemically and clinically, it might be possible that the flora in old kapok was the cause of this difference. Patients sensitive to dust brought in samples of kapok, feathers, cotton, wool, and various types of animal danders and the samples were subjected to conditions favorable to mould growth. It was shown from the culture of fifty samples that no one mould grew on all of the substances of a certain type, nor was there a single mould, or a combination of moulds, specific to the environment of any one individual patient. Although kapok grew more moulds than any other material, it did not harbor any specific mould or combination of mould spores. The authors were unable to demonstrate positive skin test reactions to the moulds in all dust cases.

In 1937, Wagner and Rackemann<sup>64</sup> again attempted to establish the nature and the cause of the antigenicity seen in old kapok and not present in new kapok. Sterilization of extracts of kapok produced no deleterious effects upon the skin active principle. Cohen's experiment with cotton linters was repeated with kapok. The fresh fibres were sterilized and kept sealed for six months, after which period it was found that there was no active principle present as evidenced by the subsequent negative skin tests. It may be emphasized at this point that in Cohen's experiments the reactions to those samples which were left in open jars were larger than those in sealed containers. Walzer also noted that Cohen used fresh material and that it was not as new as the material studied by Rackemann and Wagner. These authors discovered that heat, moisture, oxygenation and carbon dioxide did not influence the antigenic activity of fresh kapok. Moulds obtained from a batch of old kapok as well as from old cotton linters and from house dust, and incapable of giving positive skin tests were sprayed into sterile jars containing sterile fresh kapok fibre, bale cotton, and absorbent cotton. The extracts made from these materials after they have stood for sixty days gave positive skin tests, but less so than did extracts made with old kapok. As the materials stood for longer periods of time the positive skin tests produced were larger. The repetition of the experiments with *B. subtilis* resulted in skin tests which were larger than those due to the extracts listed above. The authors concluded that the breakdowns in the kapok fibre were probably due to the effect of the growth of moulds upon the kapok and that the combination of moulds and kapok gave a positive skin test, although each of the original substances might give negative tests. Since this work was done with direct skin testing and the extracts obtained with *B. subtilis* gave larger reactions than did the mould extracts, Walzer noted that the mould theory of the cause of dust sensitivity could not be finally accepted until more evidence was presented.

In their subsequent studies, Wagner and Rackemann<sup>65</sup> noted that when a patient was sensitive to any one of the four substances, namely house dust, kapok, cotton linters and chicken feathers, he was frequently sensitive to the others. It appeared that a possible inter-relationship existed between the different dusts of household origin. The sera of patients sensitive to these substances were used for passive transfer exhaustion tests with the purpose of eliciting such cross reactions as might be present. No constant relationship between the four varieties of domestic dusts was discovered. Such variations as did occur depended on the reagin content of the different sera. *In vitro* tests were equally unsatisfactory in proving cross relationships between the four substances listed. It appeared that desensitization of passive transfer sites with kapok affected the dust and feather reagins but that exhaustion of the sites with either of these substances did not fully affect the kapok reagins. A comparison of the two methods of testing by direct skin tests and by mixtures of sera and antigens revealed discrepancies which, theoretically, should not have been present. The authors concluded that kapok, cotton linters, house dust, and feathers were not identical in their biological reaction in spite of the fact that many patients reacted to all four, and that studies of cross relationships using an *in vitro* method depended

on the reagin concentration of the sera for their final results. It appeared that none of the substances contained a common principle.

Since the studies were made upon eighty allergic and thirty non-allergic individuals, the first demonstrating positive skin tests in 64 to 81 per cent and the second group in 42 to 67 per cent, Walzer<sup>66</sup> contended this was further evidence of the irritative properties of the extracts used, since the distinction between atopic and normal groups of subjects was much less definite than is generally supposed.

Pratt<sup>52</sup> was able to demonstrate reagins in twenty of twenty-five patients, but the reactions were not considered as indicating a specific hypersensitivity, but rather as due to irritation. Walzer also drew attention to the phenomenon that positive passive transfer tests did not occur as frequently with 1+ reactions in cotton linter, dust, feathers, and kapok sensitivities as it did with other antigens.

Hill<sup>42</sup>, however, considered all of the positive reactions in eczematous children as specific and not as being irritative in nature, since adequate control studies with normal infants of the same age group demonstrated no positive skin test reactions. It is generally known, however, that the infant's skin is less sensitive not only to dust but also to histamine, which again raises the question as to whether or not slight reactions to house dust and to similar dusts are specific.

Albert, Bowman and Walzer<sup>1</sup> studied fifty-four atopic individuals of whom twenty-two manifested a 1+ reaction to house dust. Of these, eighteen gave positive passive transfer reactions; twenty-four gave a 2+ reaction, of which two-thirds could be transferred, eight gave a 3+ reaction, all of which gave positive passive transfer results. In every instance in which dust reagins were present, reagins were also present to other dust producing inhalants, such as wool, feathers, or silk. In other series of ninety-seven children, seventy-two demonstrated reagins for house dust, and a positive passive transfer was present to one or more other inhalants whenever dust sensitivity existed. Reagins for pollen extracts and for foods, however, were found to occur independently of the reagins for house dust. In the following year, Walzer questioned the specific nature of dust in spite of the work listed above and concluded that the nature of the house dust antigen was unknown, since dust reactions were consistently related to positive skin test reactions to other inhalant substances. Pratt, however, was definitely able to state that in two patients of a group of fifty-six children reacting to house dust, there were reactions to house dust alone as corroborated by the presence of reagins.

Coulson and Stevens<sup>24</sup> brought a new and complicating factor into the picture by showing that there was a nonspecific substance in house dust which could be used to induce anaphylactoid symptoms in unsensitized guinea pigs. While studying anaphylactic sensitivity to a water extract of both house dust and of cotton linters as demonstrated in guinea pigs previously sensitized by subcutaneous injections of alum treated extracts, anaphylactoid symptoms were observed following an initial intravenous injection of water extract of house dust in unsensitized guinea pigs. This was interpreted by the authors as evidence of a nonspecific toxic factor present in the house dust extract.

Friedman<sup>37</sup> demonstrated in 1939, that guinea pigs sensitized with a 1 per cent alum precipitated house dust extract reacted anaphylactically in thirty to forty days to intravenous injections of house dust extract. Eighteen of twenty guinea pigs demonstrated positive Dale reactions and eleven of twelve demonstrated sensitivity by the intestinal or uterine strip technique. In eleven of twelve animals the *in vitro* test for sensitivity done on strips removed before the animal was shocked demonstrated contraction while only two of twelve animals dying in anaphylactic shock responded to house dust extract. All responded to histamine stimulation. In ten animals there was evidence of desensitization *in vivo*. Anaphylactic death could not be induced with the intravenous injection of house dust unless the dose was more than 0.1 c.c.,

but anaphylactoid reactions could be induced by intravenous injections of 1 c.c. The authors, with justice, conclude that the narrow working range between the minimal shocking dose and the dose which includes nonspecific anaphylactoid reactions is a serious handicap in the application of these techniques to the investigation of the nature of the house dust antigen.

Cohen and the co-workers<sup>20</sup> using cotton linters taken from the center of a bale of stored cotton, which therefore did not contain other epidermal substances or antigens, made a 1:50 dialyzed extract for investigative purposes. He reported that 90 per cent of his clinically dust sensitive patients gave a reaction which was 1+ or larger and that allergic individuals not sensitive to dust and normal controls gave negative skin tests. Eleven of twelve patients giving positive reactions gave 1+ or larger passive transfer reactions in the presence of completely negative controls. Using an alum precipitated extract of cotton linters, he was able to sensitize and shock guinea pigs who, reacting to cotton linters extract, could not be shocked by extracts made from cottonseed itself.

Hampton and Stull<sup>40</sup> prepared extracts made with dusts from individual sources and one from several sources. They concluded from the animal experiments that house dust extract contained an antigen other than that found in the known inhalants used for testing purposes and that this antigen was common to three different types of dust extract. In a series of 147 sensitized guinea pigs, cottonseed, cotton linters, kapok, raw silk, orris root, glue, pyrethrum, wool and other inhalants failed to produce positive Dale tests.

In an extension of their earlier work, Coulson and Stevens<sup>25</sup> thought that greater significance should be given to cotton linters as a possible source of the house dust antigen. They successfully sensitized eight guinea pigs to a water soluble antigen present in linters and failed to produce anaphylactic shock with a cottonseed extract made from the kernels of the cottonseed. The guinea pigs, however, demonstrated anaphylactic reactions to each of three different house dust extracts. Crossed reactions with extracts of house dust revealed differences in potency although there was an antigen common to all three extracts. Since the dialysates, however, were unable to produce anaphylaxis in guinea pigs sensitized to the respective extracts, the earlier work of Grove and Coca was confirmed. Crossed reactions with extracts of house dust and of cotton linters indicated that an antigen common to both might be present. Guinea pigs sensitized to house dust could be desensitized with dilute linters extract and were then incapable of being shocked with intravenous injections of concentrated linters extract. The fact that such guinea pigs could be then put into fatal anaphylactic shock with dust extract seemed to infer that beside the common antigen there might be another in house dust extracts. In several cases, fatal anaphylaxis occurred when animals sensitized to house dust extract reacted to shock doses of wool, implying that house dust extract might contain an antigen present also in wool. Since some guinea pigs sensitized to egg white were also fatally shocked by the dust extract which might, therefore, contain egg protein, the authors concluded that samples of house dust are variable and complex with respect to their antigenic content and that antigens allied to those in cotton linters, egg white, and wool were present. They were unable to demonstrate the presence of a single characteristic antigenic entity in house dust.

Davidson<sup>26</sup>, studying a group of ninety-five dust sensitive patients, compared their reactions to house dust. By skin test techniques, horse dander was the most common, single, positive reaction, followed in succession by cow dander, cat dander, cottonseed, pyrethrum, and glue. The author therefore concluded that house dust possessed an antigenicity due to the substances it contained.

In 1942, Boatner and Efron<sup>3</sup> were able to prepare allergenically potent concentrates of dust by subjecting aqueous extracts to two successive fractional precipitations

with dioxane, followed by two successive precipitations from concentrated ammonium sulfate solution, dialyzing their final substance. The purified fraction appeared as a dark brown, glossy solid completely soluble in water and exhibiting some of the chemical properties of both carbohydrates and protein.

Sutherland<sup>60</sup> reviewing the literature relating to the chemistry of allergens with special reference to house dust, described the isolation of a polysaccharide containing fraction which, after the removal of all protein, demonstrated considerable activity.

Efron<sup>28</sup> later described his house dust substance as a fine, greyish powder formed by the aging of the materials from which household articles, furniture and clothing are composed and as physically, chemically, and biologically different from the original source materials. He did not deny that samples of house dust might contain many differing substances derived from furnishings, and affirmed that the ordinary house dust extract was diluted with adulterants and that this in turn was responsible for the necessity of intracutaneous testing, since the dust possessed a low, antigenic content. This was evidenced by the infrequency of constitutional reactions.

His most recently purified house dust extract is however sufficiently potent for scratch test purposes in the greater proportion of dust sensitive individuals and evidently possesses such high antigenic content that it produces frequent constitutional reactions. With this extract, patients who have previously shown no positive skin tests have been diagnosed as suffering from respiratory tract allergy due to dust alone. In patients with multiple sensitivities, the house dust test is large, if not larger, than that produced by any of the other allergens presumably present. He infers that it is not so much that dust possesses an antigenicity due to the presence of kapok, feathers, or cotton linters, but rather, that the patients who are negative by skin test to the materials listed when new but positive to the same materials when aged, are reacting to substances which contain properties common to house dust.

No review of the subject of house dust would be complete without a brief description of the many methods by which its extracts have been made. The house dust was not only obtained from varying sources, but quite obviously must have varied in potency and in irritating qualities. The methods of preparation were so diverse that this alone might help to explain some of the confusing differences discovered in the incidence of dust sensitivity and in the varying results of investigation. The extracts used were not standardized chemically or physically and only recently has any house dust extract been standardized biologically.

Kern<sup>43</sup> used a crude alcoholic extract of dust collected from patients' homes. The material was allowed to stand for several days in 14 per cent alcohol and then filtered before use.

Coca<sup>13</sup> defatted dust with carbon tetrachloride and with ether and extracted the material in his alkaline antiseptic solution. It was concentrated by evaporation, kept acid with carbon dioxide, dialyzed against Coca's fluid, and Seitz filtered, and then tested for sterility before use. Cooke<sup>23</sup> prepared his dust extracts in essentially the same manner. Rowe<sup>55</sup> used 0.5 per cent salt solution (as suggested by Piness<sup>51</sup>), as a substitute for Coca's extraction fluid.

Spain and Newell<sup>57</sup> concentrated the allergen in house dust extract by ultra-filtration through cellophane. The residue of colloidal material left on the filter membrane contained practically all of the activity of the original extract, free from color and a great deal of the extraneous matter.

The cotton linters extract prepared by Cohen was dialyzed in a cellophane bag in running water for forty-eight hours, and the extract then passed through filter paper and subjected to Seitz filtration before being dried in 30 c.c. quantities for storage in vacuum. When required, the residue was re-dissolved in 30 c.c. of sodium chloride

(0.85 per cent) containing Merthiolate (1:20,000) and a dilution (1:50) of this solution in 0.4 per cent phenol and 0.85 per cent sodium chloride was used for intracutaneous testing. Although the technique for lyophilization is now generally known, Cohen's original paper<sup>17</sup> should be consulted for the most exact details of adapting this process for the preservation of dust and pollen extracts for the small laboratory.

Hampton and Stull<sup>40</sup> prepared their dust extracts with carbon tetrachloride. After filtration and evaporation, the dust was extracted with a mixture of sodium chloride (0.5 per cent) and sodium bicarbonate (0.3 per cent) for twenty-four hours under toluene at 7°C. The extracts are separated from the solid material by a meat press and dialyzed against water under toluene for twenty-four hours. Following the addition of sodium chloride and sodium bicarbonate, the dilution is Seitz filtered and the extract so standardized that 0.00001 mg. protein nitrogen equals one unit.

Sutherland<sup>59</sup> prepared his house dust extract by wetting 500 gms. of dust with N/10 ammonia, and allowing it to stand for twenty-four hours before wrapping the mass in cloth and squeezing it through a press. The resulting muddy fluid is filtered through paper Seitz filters until a clear yellowish filtrate is obtained. Sodium benzoate (20 gms. liter) is added. Hydrochloric acid (1:15) is then gradually added until the mixture becomes slightly acid to Congo Red. A precipitate of benzoic acid appears in twelve to twenty-four hours and is filtered off in a Burhoes funnel and allowed to dry. The active principle is said to be adsorbed on the precipitate and released when the benzoic acid is dissolved in acetone. Any remaining precipitation is removed by centrifugalization. The material is washed repeatedly in acetone and finally in dry ether and allowed to dry. The resulting brownish amorphous powder is found to show great activity and is reported as providing an ideal testing agent.

In a series of papers by Efron, Boatner, and Dorfman<sup>4,5</sup>, there is described a method of preparing house dust extracts free from large amounts of non-allergenic material. The extracts are highly purified and concentrated and are more active allergenically than any other extracts so far used. These extracts produce uniform strong positive reactions by the scratch method in clinically proven dust sensitive individuals. For the exact details of manufacture, the original papers, which are generally available, should be consulted. The dust extract is available commercially and will give positive skin tests in dilutions varying from 1:50,000 to 1:5,000,000.

Efron<sup>28</sup> has more recently described an improved method of the purification of house dust extracts based on the principles of his earlier papers, but with a slight modification. There are now available both therapeutic and diagnostic solutions, the former consisting of a glycerinated 2.5 per cent stock concentrate from which the appropriate dilutions may be prepared for treatment. The latter consists of glycerinated 0.5 per cent solution of the principal extract and as such is used for scratch testing or appropriate dilutions used for intracutaneous testing.

As regards the specificity of such extracts, Bowman and Walzer<sup>6</sup> pointed out that crude house dust extracts were irritating and that even large reactions should be read conservatively unless the presence of reagins could be demonstrated. Walzer noted that Bowman was unable to obtain completely negative skin reactions to ordinary crude stock house dust extracts by the intradermal method in a series of control patients and that further dilution of the extract to the point of dispossessing it of its irritating properties deprived it of its value as an effective diagnostic agent.

Feinberg<sup>63</sup> stated that there were no absolute criteria to determine whether or not a positive reaction to house dust represented a specific sensitivity. Efron<sup>28</sup> pointed out that the wide variations found in the incidence of house dust sensitivities were to be explained chiefly on technical differences, namely that, heretofore, house dust extracts had not been purified and standardized biologically. He stressed the fact that scratch tests as a rule did not elicit irritative reactions.

Cooke<sup>23</sup> using intradermal testing techniques found one-third of 327 cases of

hypersensitivity as due to house dust. It is interesting to note that this figure is much lower than that reported in more recent studies.

Meyer<sup>46</sup> considered house dust to be a primary factor in 57 per cent of 235 asthmatic patients as evidenced by skin tests with both stock and autogenous extracts.

Brown<sup>7</sup> was able to demonstrate positive skin test reactions to house dust in forty-seven of 100 patients presenting symptoms of bronchial asthma.

Rowe<sup>55</sup> obtained positive skin tests to house dust in 45 per cent of his patients with bronchial asthma. Two-thirds of the patients showing positive skin test reactions to dust gave histories suggestive of clinical sensitivity. A large proportion of these patients gave positive skin tests to other inhalant substances. Peshkin<sup>49</sup> (1926) summarizing the earlier work concerned with house dust, stated that he did not believe that house dust was the most important etiological agent in the bronchial asthma seen in his series of children studied. The same author<sup>50</sup> prepared house dust extract according to Coca's method and found the intradermal technique to be superior to that using the scratch type of application.

Pratt<sup>52</sup> tested seventy-one children who suffered from symptoms of perennial bronchial asthma by means of the intracutaneous method and was able to demonstrate sensitivity to house dust by passive transfer in 78 per cent of the subjects. Two of the subjects failed to react to one other substance and the author states that with multiple sensitivities present, the evaluation of house dust as a clinical cause of bronchial asthma is very difficult.

Cazort<sup>12</sup> using the intracutaneous method found that 74 per cent of 574 cases of perennial bronchial asthma gave positive tests to one or more of 140 allergens, and that about 45 per cent of this number reacted to house dust. Fourteen patients reacted to house dust alone.

Montgomery<sup>47</sup> demonstrated positive skin reactions to dust in forty-four of fifty-seven cases of bronchial asthma or 77 per cent. He described seven patients in whom the positive reactions were limited to dust alone.

Buffum and Freedman<sup>11</sup> reported 101 cases of bronchial asthma in children. Of these patients, seventy-eight had perennial bronchial asthma and twenty-three suffered from seasonal bronchial asthma. Using the scratch test method forty-five of the patients responded with positive reactions ranging from 1+ to 4+. With the crude type of dust extraction, nineteen of seventy-five reacted to autogenous dust extracts. The relationship between the dust reactions and those to other inhalants was shown by 75 per cent of thirty-four patients, who, reacting to animal inhalants, also reacted positively to dust. The nine patients who were dust negative gave weak reactions to animal inhalants, while house dust sensitive patients gave strong reactions to both house dust as well as to animal inhalants. Skin test reactions to foods occurred independently of the dust reaction. Of forty-two patients reacting to pollens, twenty-five were dust positive and seventeen dust negative. In eight patients in this series, dust alone was considered as the exciting cause of the bronchial asthma as demonstrated by the fact that improvement was immediate when the offending agent was diminished or removed. Of 101 patients, thirteen were severely asthmatic and of these, eleven gave positive house dust reactions and four were proven clinically sensitive to household dust.

An analysis of the reported incidence of specific house dust sensitization from the work of a number of investigators shows that the figure varies from 45 to 79 per cent in patients suffering from bronchial asthma.

Of interest in this regard, is the suggestion by Cazort<sup>12</sup> who states that patients with bronchial asthma, sensitive to house dust, generally seek diagnostic studies during the Fall and Winter and have their longest remissions during July and August. The patients usually give a history of prolonged nasal irritation worse at night and during the early hours of the morning. He is usually worse at home.

## PROGRESS IN ALLERGY

Efron<sup>28</sup> however felt that it was not necessary to correlate the history and the specific sensitization. It was not always possible to distinguish between the irritant and the allergic reactions following exposure to house dust and almost all patients with respiratory tract allergy are aggravated by such exposure.

In explanation of these varying previous studies, Dorfman and Efron<sup>27</sup> devoted their attention to the effect of varied dilutions of house dust extract upon the skin when the scratch method of testing is used. They found that the skin test curve obtained with serial dilutions of house dust was a discontinuous one, so that in a given subject, a given size skin reaction could be produced by potencies of extract which varied greatly. Equally sized skin reactions might denote a very wide range of potency of the extract, and a tendency toward similar sized reactions was present in the upper ranges of the concentrations used. A plateau might, however, occur at any level of concentration and with reactions of any size. The discontinuity of the skin reaction curve was obtained despite the presence of factors which affected the size of the skin reactions and which might tend to produce unequal reactions even of extracts of the same concentrations and amounts. The authors later applied the use of the comparative skin reaction curve to the determination of the skin reacting potency of house dust extracts and, using a scratch test technique, demonstrated differences in the reactivity of the skin between the radial and ulnar sides of the forearm. Dilutions of the same dust were then made and comparative skin test curves studied. Using two separate dust extracts for the dilution method and the parallel scratch test technique, it was possible to make a biological assay of the potency of the extracts.

In an extension of their studies, Pabst, Boatner, and Efron made comparative tests on forty house dust sensitive patients, using several dilutions of the identical extract and found no significant difference in the size of the reaction between the radial and ulnar sides of the forearm. Using two extracts, one of which was twice as concentrated as the other, 403 comparative skin tests were performed on fifty-five house dust sensitive patients. These tests performed by the scratch technique reveal a significant difference between the two extracts. The authors concluded that these significant differences in the sizes of the reactions when different extracts were tested were attributable to the differences in extract potencies and not to be sampling errors in the testing technique. In this paper, the authors established the use and importance of the chi-square test method for the statistical analysis of comparative skin tests. In their next successive paper, the same authors presented an extract method of estimating the probability associated with a given value of chi-square for an analysis of comparative skin test reactions.

The continuation of the work by the same authors consisted of a study made by means of the scratch test using purified house dust extract upon two groups of patients. The first, a controlled group of 200 subjects, gave negative present and past histories of any allergic symptoms. The second group consisted of 160 patients presenting symptoms of perennial hay fever or asthma or both, although in this group the symptoms were not always produced by exposure to house dust. The purpose of the tests was to establish a diagnostic efficiency of the purified dust extract referred to above. As a base line for their studies they defined their concepts which can best be given in their own words as "the presumptive evidence of sensitization to a ubiquitous substance by skin tests depends upon the demonstration of a typical skin reaction to an extract of such a substance, which extract, when applied in identical concentration and quantity in previous tests, is shown to produce a significantly greater incidence of typical skin reactions in a series of patients, whose symptoms could be attributed to that substance than in a series of individuals having no disease attributable to this substance." An irritant extract was defined as "one which produces positive skin reactions in a percentage of control cases, not significantly different from the percentage produced in patients whose symptoms are attributable

## PROGRESS IN ALLERGY

to the particular substance in question." The diagnostic efficiency of an extract depends upon the relationship of the percentage of positive reactions in these two groups.

In the control series the skin reactions with varying dilutions was found to be 7.5 per cent and in the allergic group 78.1 per cent. Dividing the sum of the two by the incidence of the allergic group results in a fraction 0.912 and suggests that a positive skin test with this extract is diagnostic of allergic disease attributable to house dust in 91.2 per cent of the instances in which the test is positive.

Further studies by the same authors<sup>33</sup> evaluated the significance of positive reactions to intracutaneous tests performed with the purified house dust extract. Two groups of patients were studied, the first, a control group of sixty-seven subjects with no history of allergy who showed no reactions to scratch tests with house dust and a second group consisting of seventy-five patients presenting perennial symptoms of hay fever or bronchial asthma or both, all of whom gave positive scratch tests to house dust extract. The tests were done intracutaneously with 0.01 c.c. quantities of concentrations ranging from 0.002 to 0.000002 per cent of the original house dust extract. The dilutions represented serial dilutions of a 0.1 per cent solution of house dust in 50 per cent glycerin containing 0.4 per cent phenol. The authors found that extracts of the house dust up to and including 0.002 per cent solutions were not irritating and the reactions produced up to the concentration of 0.002 per cent were allergenic in nature.

In the final paper of the series, Efron<sup>29</sup> presented a carefully worked-out thesis for the adoption of the biological method of standardization for house dust extracts. Since the extracts cannot be made constant in potency, are subject to deterioration, and the reactions are not at all times exactly reproducible, and since the chemical and physical measuring techniques such as the total nitrogen, the protein nitrogen, the weight by volume, or the Noon unit are, at best, not too reliable, it is best to base our criteria of the allergenic potency upon (1) the specificity of skin reactions (2) the diagnostic probability of specific skin reactions and (3) the comparative size of specific skin reactions. In considering the specificity of skin tests, one must be careful to distinguish between specific and nonspecific reactions. The latter can be due to irritation, primary urticariogenic substance content or to nonspecific properties, such as concentration or glycerin or histamine content. The difference in incidence of positive reactions in a series of allergic subjects and a group of non-allergic individuals may then be attributed to the substance itself. If the difference in the number and type of positive reactions is significant statistically, the skin reactions in both groups are considered to be specific. As an example, the following data is presented.

A solution of purified house dust (0.75 per cent) tested by the scratch test method gave fifteen positive reactions in 200 normal controls and 125 positive reactions in 160 allergic patients. Used in the same way, an ordinary house dust extract gave twenty positive reactions in thirty controls and sixty-five positive reactions in eighty allergic individuals. From the point of view of specificity of reaction, the latter series is obviously not statistically significant. Of course, another biological method of assaying solutions is an analysis of the difference in incidence of positive tests in passively sensitized sites and in the non-sensitized skin areas of control patients. In an elaboration of this point, Efron recalls that Black<sup>2</sup> first suggested that the reagin-allergen reaction is not the cause of the clinical symptoms and that it may be that some other substance is concerned in precipitating such symptoms. The following generally known phenomena attest to the fact that such a mechanism exists. It is a common experience that the incidence of specific sensitivity is significantly greater than that of clinical sensitivity. Specific skin reactions may antedate clinical sensitivity just as specific skin sensitivity may remain long after clinical sensitivity has disappeared. The symptoms of allergic individuals are

## PROGRESS IN ALLERGY

commonly intermittent. Specific reactions, therefore, may or may not be relevant to the presenting symptoms. Those that are relevant are the diagnostic reactions, which constitute the clinically significant fraction of the total number of specific reactions.

The problem is by no means susceptible of simple solution. The observation that when comparing two extracts the skin tests may be larger, smaller, or of equal size, is not always an indication of the difference in the two extracts. The papers quoted actually state that "the curve of skin reaction sizes from different serial dilutions of an extract tend to plateau." For a given substance, a skin reaction of a given size can be produced by varying concentrations of the same extract, just as equally sized reactions may occur from extracts which vary widely in potency. Only differences of certain magnitudes are demonstrable by means of comparative skin tests. The authors show that when one extract has twice or more the potency of another, comparative skin tests reveal a difference. Whether or not smaller degrees of potency difference between two extracts are demonstrable by comparative scratch tests has not as yet been determined.

The studies mentioned would have little or no significance unless they could be correlated with the results of treatment, either passive, as by the elimination of the offending antigen or active, as by injection therapy.

Kern<sup>43</sup> presented a case of a thirty-six-year-old woman with symptoms of asthma present for fourteen years, perennially, and most marked during August and September. Skin tests were present to an extract made from her cotton mattress and to pollen extracts. On advising the patient to wrap the mattress with heavy paper there was prompt relief of symptoms. Whenever it was suspected that the offending agent was in the room of the patient with asthma, Kern suggested the removal of the furniture from the room with replacement of individual items over a period of time, in which manner the offending agent could easily be discovered and discarded.

In another of the early classic cases, Cooke<sup>23</sup> presented a twenty-eight-year-old male patient with asthma of fourteen years' duration whose skin tests were negative to extracts of the common emanations but whose symptoms were completely environmental in that they always occurred upon his return home. Extracts of dust from the patient's household gave positive intradermal tests. The author states that the failure of treatment of patients with multiple sensitization may be explained by the discovery of an exact single etiological agent.

Leopold and Leopold<sup>45</sup> were able to produce asthmatic attacks at will in a dust sensitive individual under controlled conditions of humidity, temperature, and barometric pressure. They found that the effects of these latter three factors were negligible.

Feinberg<sup>34</sup> presented four patients with bronchial asthma sensitive to house dust, all of whom responded favorably to hyposensitization.

Cohen<sup>18</sup> described the use of the mechanical air filter placed in the patient's home to make room pollen free as well as dust free. The filter proved to be satisfactory in removing 99 per cent of the pollen particles.

Brown<sup>8</sup> reported that in patients with bronchial asthma who were sensitive to cottonseed and to kapok the removal of the offending articles and their associated dust content brought on prompt relief.

Rowe<sup>55</sup> noted the value of testing with house dust extract as an indication of the type of sensitization causing the patient's condition. He felt that reactions due to house dust extract should make the physician suspicious of sensitization to other inhalants.

Cohen and Rudolph<sup>19</sup> reviewing 100 patients presenting ragweed hay fever reported that 30 per cent had slight symptoms at other times of the year. Of these patients, 70 per cent had seasonal symptoms only, and 36 per cent were sensitive to

## PROGRESS IN ALLERGY

substances other than ragweed pollen. It was concluded, therefore, that in the treatment of patients with ragweed hay fever other sources of sensitivity had to be eliminated or treated. In another paper, the same authors outlined a program for the treatment of dust sensitive asthmatic patients calling for the elimination of many sources of dust as possible. The elimination of the dust by daily cleaning was to be accompanied simultaneously with hyposensitization therapy.

Cazort<sup>12</sup> also recommended avoidance of dust during desensitization, the best results being obtained in the patients who gave the most strongly positive skin reactions. The poorest results were achieved in those patients who had chronic vasomotor coryza and slight skin reactions.

Todd<sup>61</sup> found the use of an autogenous dust extract more satisfactory than stock dust and claimed good to excellent results in over 70 per cent of his patients.

Buffum<sup>10</sup> reviewing sixty-four cases of bronchial asthma given general treatment and dust elimination, but no hyposensitization reported that 18.8 per cent presented no symptoms for one year, 43.8 per cent were much improved, if not almost entirely relieved, 31.2 per cent were improved, while 6.2 per cent were unimproved.

Montgomery<sup>47</sup> reported on the studies of fifty-seven cases of bronchial asthma over a two-year period of whom forty-four were skin sensitive to house dust extract. Of this number, thirty were chosen for study, since they had been under treatment for more than one year. Of these, eleven showed associated food sensitivities, six pollen sensitivities, and ten chronic infection. The patients were treated by elimination, pollen therapy, vaccine therapy and hyposensitization to house dust extract. Sixteen were completely relieved, seven markedly benefited, three achieved fair results, and four reported as complete failures. Montgomery concluded that house dust sensitivity was a common cause of bronchial asthma and in spite of frequent complications with other forms of allergy, good results could be obtained by suitable treatment.

Sutherland<sup>59</sup> desensitized twenty asthmatic soldiers with a 1 per cent solution of his house dust extract, the initial dose being 0.05 c.c. with increases at weekly intervals so that improvement of symptoms could be noted after twelve injections.

Efron and his colleagues<sup>31</sup> reported on the studies of seventy-two patients who suffered from bronchial asthma and hay fever from early September to the end of the following June, reporting freedom from symptoms during the summer months. All of the patients gave positive skin tests to purified house dust extract, and were treated with hyposensitization therapy over a period of nine to eighteen months. Treatment was initiated with 0.1 c.c. of a 0.0005 concentration of purified house dust, the increases being given according to the patient's tolerance with intervals from every two days to once weekly. Those patients who showed a moderate to marked improvement were little affected by weather. Local reactions were frequent and twelve of the patients experienced a total of eighteen constitutional reactions, the majority occurring in three. Dust elimination instructions were intentionally omitted as part of the program. In this group, thirty-seven (over 50 per cent) showed marked improvement; twenty-four (33 per cent) reported moderate improvement, six slight improvement, and five no change. The authors concluded that these results further established house dust as an important etiological factor in the causation of this type of bronchial asthma. Since the dust extract used in this work is commercially available, confirmation of these results is to be expected.

It is apparent from this review of the subject that dust sensitivity is common and that solutions made by many differing methods are effective in detecting such sensitivity and in treating it. When present, dust sensitivity is usually corroborated by the common criteria which may be listed as positive skin and passive transfer tests, improvement following elimination or injection therapy, which may be accompanied by constitutional reactions.

## PROGRESS IN ALLERGY

This review was written as a first part of the study of the background of the subject since no work had been done with the object of detecting the presence or absence of skin blocking antibodies as additional evidence of a somatic response to injection therapy. With the standardized solution as potent as that prepared by Efron, it was obvious that this would necessarily be one of the next studies to be done in this field. This work, dealing with immunological factors, and now in progress, will be published in the near future.

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## IN MEMORIAM

formity caused by nasal allergy which is known as the allergic facies. He first described soy bean as an important source of allergy. He was the first to do pollen counts in the Middle West and was the inventor of a machine and method for rapid and accurate determination of the pollen count in the air. In 1923 he persuaded Oren C. Durham, now a nationally known authority on pollen, to give up his work as a photographer and devote all of his time to the collection and study of pollens and set up a botanical garden where Durham's original pollen studies were made. He gave the first Allergy Exhibit at the Scientific Exhibit of the American Medical Association and was awarded the Silver Medal for Research in Allergy in 1924. He was president of the Association for the Study of Allergy in 1925. He received the Forum of Allergy Award for Distinguished and Original Contributions to the Field of Allergy in 1942.

He was a fellow of the American College of Physicians, an Honorary Fellow of the American College of Allergists, fellow of the American Academy of Allergy and a member of many other medical societies. He was the author of "Oral Sepsis in Relation to Systemic Disease" in 1918. He wrote the chapters on Allergy for the *Cyclopedia of Medicine*, *The Practitioner's Library of Medicine and Surgery* and *The Modern Home Medical Adviser*. He wrote the *Annual Review of Literature in Allergy* as related to Otolaryngology for the *Journal of Otolaryngology* from 1926 to 1938. He presented the Allergy and Physical Allergy Exhibit in the Hall of Science at the Century of Progress in Chicago in 1933 and 1934.

He is survived by his wife, Mrs. Frances Duke, and by two children, Henry Basil Duke and Suzanne Duke Scott.

Doctor Duke was gifted with a foresight in medicine that occurs but rarely. Much of his monumental work was so far ahead of his time that it was greeted with doubt and often derision. He had the courage of his convictions and lived to see his observations acclaimed and made part of the great contributions to medicine. He was original in his thinking and possessed of tremendous physical and mental energy. It will be many years before another of his talents appears.

C. M. K.

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## PROGRESS IN ALLERGY

(Continued from Page 240)

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# News Items

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## MARCELLE HYPO-ALLERGENIC COSMETICS, INC., ADDITIONAL GRANT

The College gratefully acknowledges receiving the sum of \$500 for a Merit Scholarship Fund. This fund is to defray the attendance fee at any of the College Instructional Courses of residents or interns who are recommended by the committee for that purpose.

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Ralph I. Alford, M.D., announces his return to the civilian practice of Allergy at his former location, 83 Park Street, Montclair, New Jersey.

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Dr. Marion T. Davidson announces his return from military service to the practice of allergy, 819 Frank Nelson Building, Birmingham, Alabama.

\* \* \*

Myron A. Weitz, M.D., and Louis E. Lieder, M.D., announce their return from military service and association in the practice of allergy at 327 Osborn Building, 1021 Prospect Avenue, Cleveland 15, Ohio.

\* \* \*

Carl D. Marsh, M.D., F.A.C.A., announces the opening of his office for the practice of allergy and dermatology at 616 Goodwyn Institute Building, Third and Madison, Memphis, Tennessee.

\* \* \*

Dr. Joseph L. Vinocur announces his return from military service and the resumption of the practice of allergy. He will be associated in practice with Dr. Benjamin Nozik, who expects to be released from the service in the very near future.

\* \* \*

Stanley F. Hampton, M.D., announces his return from military service and the reopening of former office for the practice of allergy and internal medicine, at 1018 Beaumont Medical Building, 3720 Washington Boulevard, St. Louis, Missouri.

\* \* \*

*Acta Paediatrica*, published in Stockholm, is now in our exchange library. This contains excellent articles on allergy in children. The articles are in English, and are available to the College members for review.

\* \* \*

We welcome the new *Journal of Geriatrics*, devoted to research and clinical study of the diseases and processes of the aged and aging. Volume 1, Number 1, January-February, 1946, has been received by the College library. There is an excellent article in it on "Bronchial Asthma with Special Reference to Its Elderly Victims," by Jonathan Forman, M.D., F.A.C.A.

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The attention of the readers of the ANNALS is called to the *Bulletin of Allergy*, which is devoted exclusively to the subject of allergy, and is published bi-monthly by Wyeth, Inc., and distributed to the members of the medical profession. Volume 1, Number 1, appeared in February, 1945. The cover of each issue has a portrait of the pioneers in allergy, together with a biographical sketch; there is one leading article in each issue on the various allergic diseases with a bibliography, followed by allergy abstracts.

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Dr. Harold Abramson of New York City, who served as a Lieutenant Colonel, Chemical Warfare Service, United States Army, has been awarded the Legion of Merit for his work in the Chemical Warfare Service. He was Chief of the

## NEWS ITEMS

Physical Chemical Section, Chemical Research Branch, and Assistant Chief, Defense Materiel Branch at Edgewood Arsenal, Maryland, from July, 1942, to December, 1943.

Dr. Abramson is responsible for the successful development of penicillin aerosol.

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Drs. W. Randolph Graham and J. Warrick Thomas have announced establishing the Graham-Thomas Clinic, 201 West Franklin, Richmond, Virginia, which was formerly the Vaughan Memorial Clinic. Their practice is limited to allergy and internal medicine, and the new organization will offer recognized postgraduate training in allergy for qualified physicians and will also continue the training school for allergy technicians as they formerly did. They will continue to have the same location and are making arrangements to enlarge the clinic by taking over more space.

\* \* \*

We are pleased to announce the return from service of the following members of the College and their present locations: Major Glen I. Allen, 101 Cole Court, Peoria, Illinois; Captain Maurice C. Barnes (MC), 1310 Austin Avenue, Waco, Texas; Lt. Comdr. Norman W. Clein (MC), Children's Clinic, 1155 10th Avenue North, Seattle, Washington; Captain Julius J. Greenberg (MC), 3328 Fullerton, Detroit 6, Michigan; Captain George F. Hieber (MC), 5204 Tenth Street, St. Petersburg, Florida; Captain William Jacobs (MC), 1030 Stuyvesant Avenue, Irvington 11, New Jersey; Captain Meyer R. Lichtenstein, 1733 20th Avenue, Oakland 6, California; Captain David Mansowit (MC), Uptown Bank Building, 4753 Broadway, Chicago, Illinois; Major Carl D. Marsh, 616 Goodwyn Institute Building, Memphis 3, Tennessee; Major Raymond R. Preefer (MC), 470 Westminster Road, Brooklyn, New York; Major Nathan Schaffer (MC), 172 Arlington Avenue, East Orange, New Jersey; Captain Joseph L. Vinocur (MC), 10535 Carnegie Avenue, Cleveland, Ohio.

\* \* \*

A Pediatric Postgraduate Conference was held at the University of Texas School of Medicine, Galveston, Texas, on April 15 to 20, 1946; the course was sponsored by the University of Texas School of Medicine Committee on Postgraduate Education, Dr. George M. Decherd, Jr., Director. Distinguished guest speakers included the following: Dr. John A. Anderson, Professor and Head, Department of Pediatrics, University of Utah School of Medicine, Salt Lake City, Utah; Dr. Ralph Bowen, Associate Professor of Pediatrics, Baylor University School of Medicine, Houston, Texas; Dr. Daniel C. Darrow, Associate Professor of Pediatrics, Yale University School of Medicine, New Haven, Connecticut; Dr. J. H. Park, Jr., Professor and Head, Department of Pediatrics, Baylor University School of Medicine, Houston, Texas; Dr. Ralph Platou, Professor and Head, Department of Pediatrics, Tulane University School of Medicine, New Orleans, Louisiana; Dr. George Salmon, Associate Professor of Pediatrics, Baylor University School of Medicine, Houston, Texas; Dr. A. V. Stoesser, Associate Professor of Pediatrics, University of Minnesota School of Medicine, Chief of Pediatric Service, Minneapolis General Hospital, Minneapolis, Minnesota; Dr. James Watt, Surgeon, U. S. Public Health Service, Quarantine Station, Algiers, Louisiana. In addition to the guest speakers, twenty-nine faculty members of the University of Texas School of Medicine participated.

# BOOK REVIEWS

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FAMILIAL NON-REAGINIC FOOD ALLERGY. Arthur F. Coca, M.D. 2nd ed. 202 pages. 18 tables. 11 charts. Price \$3.75. Springfield, Illinois: Charles C. Thomas, 1945.

The author has presented a concept of almost all non-infectious diseases that will, in succeeding years, either revolutionize the theory of a great part of medicine, or be buried in the files of "disproved after competent trial." To a very few who have given the time and thought necessary to the identification and elimination of allergenic substances, it seems that the author has justifiable enthusiasm for his contention.

The classification of allergic diseases is concisely reviewed, and especially is the "idioblapsis" or "familial non-reaginic" phase of food allergy forcefully presented as a new category of familial allergic diseases. The statement is made that the essential difference from the atopic category, is that this allergic reaction "practically always causes an acceleration of the pulse." A controversial issue arises here, since one must then assume that the cardiovascular mechanism is invariably sensitized. The author states that in ten years he has found no exception. Others believe they have found a rare exception. This is the new and necessary method of identifying the offending substance. Detailed explanation of the pitfalls one should expect to encounter in the use of this method, such as extraneous influences on the pulse rate, and especially "the latent period of lost sensitivity, recurrent reaction, major and minor reactions, depression of reactivity of shock tissue by single and rapidly repeated allergic reactions, sensitivity to a large number of important foods, and sensitivity to unavoidable inhalants, known or unknown," are given. This is the "meat" of the application of the "specific pulse reaction." Nearly all failures in this method may be traced to incomplete understanding of these chapters.

Biologic groupings of foods are given with a warning that few may be grouped as allergenic and that most must be tested separately.

Sympathectomy as an aid is considered, not only in its relation to hypertension, but as a valuable adjunct in other possible manifestations of allergy. From the author's experiences it diminishes not only the expressions of allergy, but in some cases entirely eliminates the expression. The physiological basis is not clear since it appears that the simple interruption of the autonomic pathway produces comparable results to more radical procedures. More complete knowledge of the entire function of the autonomies is necessary before this procedure will be used without hesitancy. Likewise, the mechanism of idioblaptic allergy is difficult of explanation, inasmuch as it is impossible to demonstrate a specific antibody. Similarly the histamine theory is held explanatory for the classification of allergens into major and minor groups, with the explanation that insufficient experimental work is available for a firm background.

Discussion, with pulse recordings on non-allergic individuals, is given in support of the author's contention that the human heart rate is remarkably constant no matter what the environmental influences. When any marked degree of variability occurs, allergic influence must be the primary consideration.

The relationship of idioblaptic allergy to hypertension, and its possible predisposing influence on the common cold are detailed with fair clinical and statistical evidence to support the conclusions arrived at. The coincidence of inconstant heart rate in those with carcinoma of the breast and in certain types of psychosis is also presented as suggestive evidence of a possible allergy factor. Obviously, years of clinical investigation will be required to furnish adequate proof of the relationship of these disorders.

M.G.M.

**TRAUMA IN INTERNAL DISEASES.** With Consideration of Experimental Pathology and Medicolegal Aspects. By Rudolf A. Stern, M.D., with a foreword by Francis Carter Wood, M.D. 575 pages, 20 chapters. Price \$6.75. New York: Grune and Stratton, 1945.

The author has accomplished a difficult task well. Controversial medical testimonies are common when trauma is claimed as the cause of an internal disease rather than a surgical condition. Appreciating the necessity of a comprehensive knowledge of a vast, accumulating literature, both experimental and clinical, on the subject, which would be invaluable to the physician required to present sound medical testimony which aids justice in determining the truth, the writer has spared no effort to make available specific and detailed knowledge of the subject.

The chapters present an unbiased analysis of trauma in the etiology of internal diseases. Occupational diseases are not included in the scope of the book.

The increasing incidences of accidents and the rapid spread of accident insurance justifies a fair and thorough discussion of the development of all traumatic diseases as this text presents it.

Practitioners and specialists alike will find this book most valuable as a ready reference book when called upon to testify concerning possibility of trauma causing or aggravating internal diseases.

There is an exhaustive bibliography of forty-two pages. The book is well bound, the paper of good quality and the print very readable.

F.W.W.

**SYMPTOMS OF VISCERAL DISEASE.** Sixth Edition. By Francis Marion Pottinger, M.D. 442 pages. 87 illustrations, 10 color plates. Price \$5.00. St. Louis: The C. V. Mosby Company, 1944.

The increasing interest in visceral neurology is attested by the appearance of a sixth edition of this remarkable text.

Symptoms of a reflex nature are sometimes most difficult to understand by the clinician because of their lack of understanding of the underlying physiologic mechanisms involved. The author attempts to correlate the clinical symptoms with clinical physiology in a manner which will help the physician to an accurate interpretation of the symptoms of visceral disease.

He describes the relationships between visceral and somatic conditions with neurons originating in the various cord segments. A better understanding of these segmental relationships and of the physiologic reflexes of visceral or somatic diseases is of inestimable value to the clinician. Although the author emphasizes the importance of reflexes, he broadly considers the physical, psychical, physiologic and pathologic influences which cause a variability of symptoms.

The monograph is arranged in three parts: Part I. The Vegetative Nervous System; Part II. The Relationship between the Vegetative Nervous System and the Symptoms of Visceral Disease; Part III. Innervation of Important Viscera with a Clinical Study of the More Important Viscerogenic Reflexes.

To the allergist the author's introductory remarks on the physical and psychic activities which change body control; the chapter on Subdermal Structures; and his discussion on page 171 of allergic inflammation are of particular interest.

However, the practical application of the principles of visceral neurology to the various diseases encountered in clinical medicine makes this monograph essential to the general practitioner as well as to all specialists who properly consider the human body as a unit.

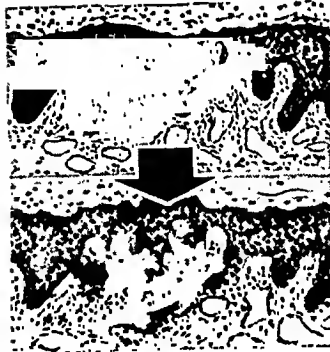
The publishers should receive credit for the good binding, the fine paper stock and illustrations at a time when material and personnel were at a premium.

F.W.W.



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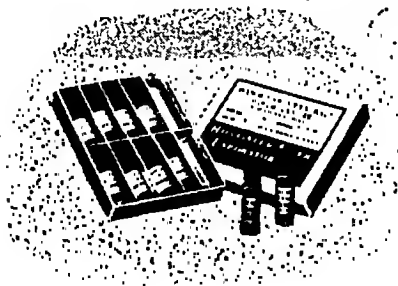


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\*Halpin, L. J.: Letter to International  
Correspondence Club of Allergy, 1943

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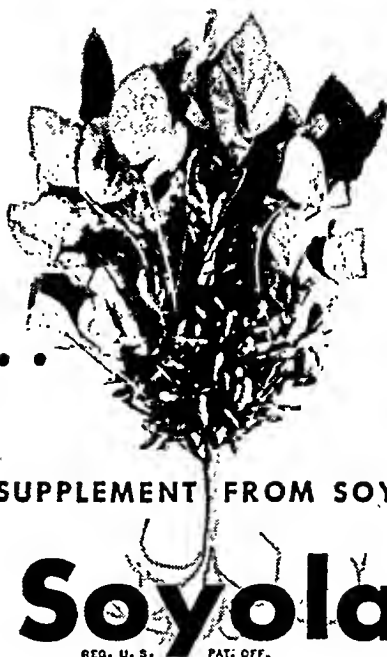
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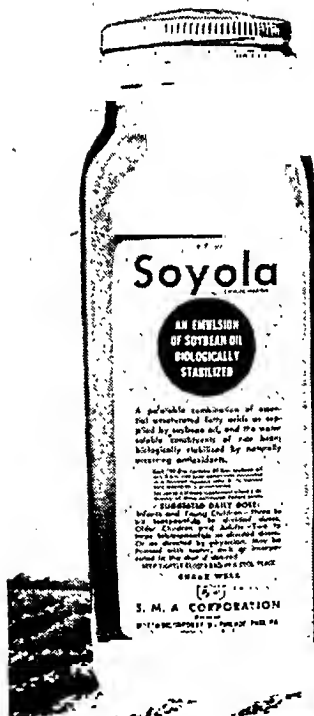
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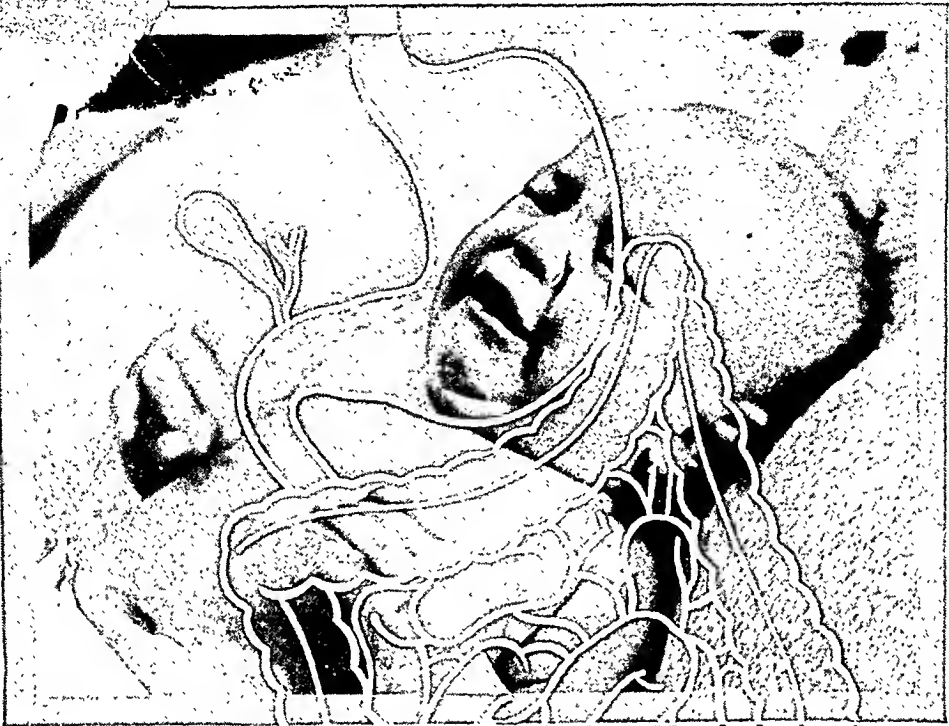
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\*Rubin, M. I., in: Mitchell-Nelson Textbook of Pediatrics, 4th ed., p. 1261, Saunders 1945

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Annals of Allergy is published bimonthly by the American College of Allergists. The contents of the journal consist of contributions in the field of diseases of allergy, book reviews, a current bibliography, editorials, case reports, new suggestions, questions and answers, news items and matters concerning the affairs of the American College of Allergists.

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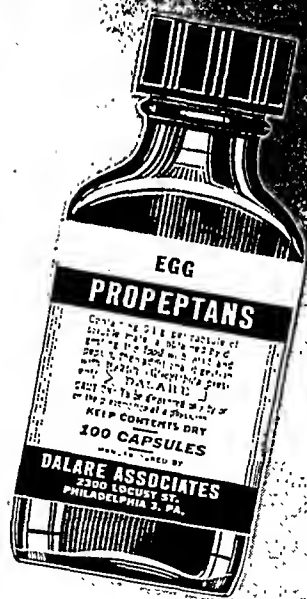
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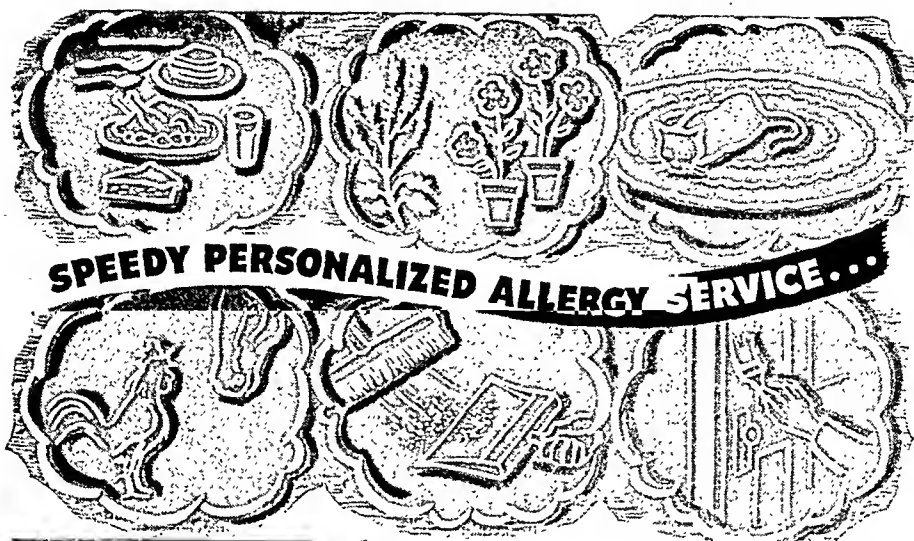
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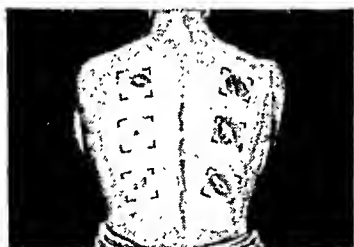
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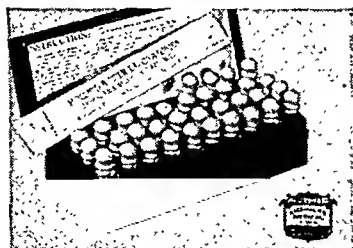
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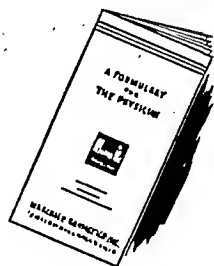


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## Contents for July-August, 1946

### BRONCHIAL ASTHMA IN THE YOUNG MALE ADULT.

*Frank L. Rosen, M.D., Newark, N. J.*..... 247

### INFLUENCE OF THE LIVER IN ANAPHYLACTIC SHOCK.

*Alfonso Graña, M.D., Rochester Minnesota*..... 261

### MANGO DERMATITIS AND ITS RELATIONSHIP TO POISON IVY HYPERSENSITIVITY.

*Harry Keil, M.D., David Wasserman, Ph.D., and Charles R. Dawson, Ph.D.,  
New York City*..... 268

### SOME CLINICAL OBSERVATIONS ON THE USE OF BENADRYL FOR THE SYMPTOMATIC RELIEF OF ALLERGIC CONDITIONS.

*L. C. Todd, M.D., Charlotte, North Carolina*..... 282

### BENADRYL IN THE TREATMENT OF ERYTHEMA EXUDATIVUM MULTIFORME.

*Hermann Pinkus, M.D., Monroe, Michigan*..... 288

### FALL GRADUATE INSTRUCTIONAL COURSE IN ALLERGY.....Facing page 290

### SENSITIVITY TO THIAMINE HYDROCHLORIDE.

*H. T. Engelhardt, M.D., F.A.C.A., and V. C. Baird, M.D., Houston, Texas*.. 291

### MALARIA AND URTICARIA.

*Major Harold H. Golz, MC, F.A.C.A.*..... 293

### GENERALIZED CHRONIC DERMATITIS DUE TO TATTOO.

*Boen Swinny, M.D., F.A.C.A., San Antonio, Texas*..... 295

### EDITORIAL:

The San Francisco Convention..... 297

Fall Graduate Instructional Course in Allergy..... 298

### PROGRESS IN ALLERGY: ..

#### Bronchial Asthma: Annual Critical Review of Recent Literature.

*Leon Unger, M.D., F.A.C.A., Chicago, Illinois*..... 299

NEWS ITEMS ..... 335

BOOK REVIEWS ..... 337

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Volume 4

July-August, 1946

Number 4

## BRONCHIAL ASTHMA IN THE YOUNG MALE ADULT

A Study of 100 Hospitalized Patients in An Army General Hospital,  
with Special Reference to Nasal Symptoms and Findings

FRANK L. ROSEN, M.D.†  
Newark, New Jersey

THE allergy ward of an Army General Hospital offers an unusual opportunity to study the early manifestations of disease. In the Army a soldier is either fit for duty or he is hospitalized. As a result, these patients can be followed more closely than in civil life, where the majority would have had outpatient status.

In this series of 100 consecutive cases admitted to the Allergy Ward of Wakeman General Hospital, Camp Atterbury, Indiana, from June, 1944, to March, 1945, criteria for diagnosis of bronchial asthma were: objective wheezing together with lung findings of prolonged expiration and persistence of generalized expiratory râles after cough.

It must be remembered that this study deals with a group of men inducted into the Army after receiving an initial physical examination. There were no cases of cardiac asthma or emphysema. One patient had a coincident asthmatic bronchitis. There were no deaths in this series and the average hospital stay was one month.

Chiefly for the purpose of disposition, the group was divided as follows:

1. Mild asthma—19 patients
2. Moderate—74 patients
3. Severe—7 patients

The latter two groups received a medical discharge; the first were put on limited duty status if their services were valuable to the Army, otherwise they were medically discharged also.

Classified "mild" were those who had occasional mild attacks of asthma not requiring adrenalin. Termed "moderate severe" were patients who

†Formerly Captain, MC, and Chief of Allergy Section, Wakeman General Hospital, Camp Atterbury, Indiana.

required adrenalin injections for relief of symptoms at one time or another during their hospital stay. "Severe" were the asthmatics who had "status" attacks, received aminophyllin intravenously in addition to other measures.

## AGE OF GROUP

Patients were all enlisted men, their ages ranging from eighteen to thirty-nine years, the average age for the group being twenty-six years. Zanfagna<sup>21</sup> reports average age of twenty-eight years in his series at an Army hospital. The average age of the nineteen mild asthmas was twenty-five years, the seven severe asthmas twenty-three years.

## RACE OF GROUP

Ninety-three white patients and seven negroes were represented, or 7 per cent negroes. The hospital as a whole averaged 4 per cent negroes for the same period. In Lieder's<sup>11</sup> series at another Army general hospital, 6 per cent were colored. Rudolph<sup>17</sup> reports 13 per cent negroes in his series.

## AGE OF ONSET OF ASTHMA

0- 2 years .....	12
2-12 years .....	30
13-18 years .....	11
19-39 years .....	47

Fifty-three patients had a history of asthma before eighteen years of age. Three of the above patients date their asthma following attacks of pneumonia in childhood. Two patients state asthma started a few months after fracturing their noses. In a series of 222 male patients with asthma comprising all age groups reported by Unger and Wolf<sup>10</sup>, 136 date the onset of their asthma before their twentieth birthday. In Lieder's<sup>11</sup> series, 75 per cent dated the onset of asthma before induction into the Army.

## SEASONAL VARIATIONS

1. Perennial—87 patients
  - (a) No seasonal variations.....60
  - (b) Worse in winter .....14
  - (c) Worse in summer and fall .....11
  - (d) Worse in spring and fall ..... 1
  - (e) Worse in spring ..... 1
2. Seasonal only—13 patients
  - (a) Late summer and fall .....11
  - (b) Spring and summer ..... 2

The high number of pure ragweed asthmas and ragweed-aggravated asthmas can be explained by the fact that many of these patients from homes in different parts of the United States were hospitalized during the ragweed season near Indianapolis, Indiana, an area which has the highest reported<sup>3</sup> ragweed pollen count in the United States.

Of the eighty-seven patients in the perennial group, fifty-five stated asthma attacks were brought on by exertion. Thirty-seven said attacks were precipitated or coincident with a "cold."

## ASSOCIATED NASAL SYMPTOMS

Forty-five patients had no nasal symptoms at the time of admission or in their past histories other than a rare cold. Fifty-five patients had either perennial or seasonal nasal symptoms on admission or past nasal complaints (stuffed nose, sneezing, itching, nasal discharge) of intensity and duration sufficient to warrant a diagnosis of hay fever or perennial nasal disease.

## SEASONAL VARIATION OF NASAL SYMPTOMS

## Fifty-Five Asthma Patients

1. Perennial—30 patients
  - (a) No seasonal variation ..... 19
  - (b) Worse in winter ..... 4
  - (c) Worse in summer and fall ..... 6
  - (d) Worse in spring ..... 1
2. Seasonal only—25 patients
  - (a) Summer and fall ..... 18
  - (b) Spring ..... 5
  - (c) Summer ..... 2

In a series of 141 asthma cases of all age groups, Schwartz<sup>18</sup> reports twenty-four with perennial nasal symptoms and twenty with seasonal hay fever.

TABLE I.  
AGE OF ONSET OF NASAL SYMPTOMS AND ASTHMA IN  
TEN PATIENTS WITH CONCOMITANT SEASONAL  
ASTHMA AND HAY FEVER

Case Number	Present Age	Age of Onset of Asthma	Age of Onset of Hay Fever
24	22	Childhood	Childhood
28	18	10	10
36	25	25	15
37	24	24	23
38	22	22	10
39	31	31	23
40	27	10	5
41	20	20	15
42	21	21	8
43	21	21	16

Eight of these ten patients (Table I) had hay fever (fall) from one to thirteen years before developing asthma. Two patients had the onset

## BRONCHIAL ASTHMA—ROSEN

TABLE II

AGE OF ONSET OF NASAL SYMPTOMS AND ASTHMA IN FIFTEEN PATIENTS  
WITH PERENNIAL ASTHMA AND SEASONAL HAY FEVER

Case Number	Present Age	Age of Onset of Perennial Asthma	Age of Onset of Seasonal Hay Fever
14	31	22	26
16	27	27	Childhood
30	20	10	10
35	37	25	25
50	22	14	14
53	38	6	6
54	32	5	26
59	19	10	10
61	38	8	Childhood
63	18	11	11
70	24	16	Childhood
71	38	37	37
72	21	21	21
80	35	25	Childhood
81	31	26	26

of hay fever and asthma together. First attack of asthma occurred at this camp (Indiana) in seven of these ten ragweed asthmas. All came from areas with less exposure to ragweed in previous years. It was interesting to note that of the thirteen pollen asthmas (eleven ragweed, two grasses), three had no concomitant hay fever symptoms.

Nine of these fifteen patients (Table II) had their first attack of seasonal hay fever and perennial asthma during the same year. In two cases the asthma preceded the hay fever by several years. In four the hay fever preceded the asthma by many years.

Fourteen of these patients (Table III) date the onset of their perennial asthma and perennial nasal symptoms concomitantly. Nine of the thirty patients had their asthma many years before nasal symptoms appeared. In seven cases the nasal symptoms appeared years before the asthma.

Thus it would seem, from a review of Table II and III, that in this series the perennial type of asthma, when present together with nasal symptoms, is for the most part initiated by both symptoms at or about the same time (twenty-three of forty-two patients). In the remaining nineteen patients of the perennial asthma group, nine had the onset of asthma one to twenty-one years before the nasal symptoms, and ten had the onset of nasal symptoms one to fifteen years before the asthma.

All of these 100 asthma patients were examined in consultation by the chief of the ear, nose and throat section\* and received a routine x-ray

\*The writer is indebted to Major J. Drucker, American Board of Otolaryngology.

TABLE III

AGE OF ONSET OF NASAL SYMPTOMS AND ASTHMA IN THIRTY PATIENTS  
WITH PERENNIAL ASTHMA AND PERENNIAL NASAL SYMPTOMS

Case Number	Present Age	Age of Onset of Perennial Asthma	Age of Onset of Perennial Nasal Symptoms
1	22	Childhood	Childhood
3	18	Infancy	Childhood
7	32	31	17
12	39	38	36
18	36	32	32
19	23	14	14
20	21	20	20
22	20	20	Childhood
23	33	Childhood	Childhood
33	18	Infancy	Childhood
46	32	22	22
49	27	26	26
52	33	29	29
55	25	21	Childhood
60	24	12	12
62	33	17	30
65	27	25	27
66	18	15	16
73	27	7	7
74	26	Infancy	Childhood
76	25	25	25
77	29	27	19
82	21	12	12
83	33	25	25
87	27	Infancy	Infancy
91	34	32	19
94	21	12	Childhood
97	27	6	Childhood
98	29	Childhood	24
100	26	Infancy	23

of the chest and sinuses interpreted by the chief of the x-ray section.\* Table IV reports their findings.

The nasal mucosa (column 1) is reported positive (*P*) if it presented an allergic appearance; i.e., pale, boggy, often with polyps or polypoid changes.

Transillumination of sinuses (column 2), although many ear, nose and throat specialists feel that this procedure is valuable only when it is negative, was performed routinely. A (*P*) report usually showed dark-

\*The writer is indebted to Major A. Gallucio, American Board of Radiology.

# BRONCHIAL ASTHMA—ROSEN

TABLE IV—PART I

FINDINGS IN FORTY-FIVE ASTHMA PATIENTS WITH NO NASAL SYMPTOMS

Case Number	Nasal Mucosa	Trans-illum. of Sinus	X-ray of Sinus	Negative Skin Tests	Blood Eosin
2	—	—	—	—	—
4	—	—	—	—	P
5	—	—	P	—	—
6	—	—	P	—	—
8	—	—	P	—	—
9	—	P	—	—	P
10	—	—	P	—	—
11	—	P	P	—	P
13	—	—	—	N	—
15	P	P	—	—	—
17	—	P	—	—	—
21	P	P	P	—	—
25	—	—	—	—	—
26	—	—	—	—	—
27	—	—	P	—	—
29	—	—	—	—	—
31	—	—	—	—	P
32	—	—	P	—	—
34	—	P	P	—	—
44	—	—	—	—	—
45	—	—	P	—	P
47	—	—	—	—	P
48	—	—	P	—	—
51	—	—	—	—	—
56	—	—	—	—	—
57	—	—	P	N	—
58	—	P	P	—	—
64	P	P	P	—	P
67	P	—	P	—	—
68	—	P	P	—	—
69	—	—	P	—	—
75	—	—	P	N	—
78	—	P	P	—	—
79	P	P	P	N	—
84	P	—	—	N	—
85	—	—	P	—	—
86	P	—	P	—	—
88	—	P	P	—	P
89	—	—	P	—	—
90	—	—	P	—	—
92	—	P	—	N	P
93	—	—	P	N	—
95	—	P	—	—	—
96	P	—	—	—	P
99	—	—	P	—	P

ness of one or both maxillary sinuses. A few cases had a cloudiness of frontal sinuses together with maxillary antra, one had frontal involvement alone.

X-ray of sinuses (column 3) was reported positive (*P*) when there was a definite thickened mucoperiosteal membrane, fluid level, polyps, mucocoele, definite cloudiness of sinus, opaque sinus. Usually both antra were involved, occasionally frontals and ethmoids. When the initial sinus plate was reported as positive, it was rechecked in one to two weeks. A few patients showed some changes in plates due to transitory sinus edema. Only one patient in this series had definite clinical symptoms of sinusitis.

In the interpretation of the sinus x-ray reports, it must be remembered that many normal individuals show abnormal x-ray findings indicating

## BRONCHIAL ASTHMA—ROSEN

TABLE IV—PART II

FINDINGS IN FIFTY-FIVE ASTHMA PATIENTS WITH NASAL SYMPTOMS

Case Number	Nasal Mucosa	Trans-illum. of Sinus	X-ray of Sinus	Negative Skin Tests	Blood Eosin
1	P	—	—	—	P
3	—	—	P	—	—
7	—	P	—	—	—
12	—	P	P	—	P
14	—	P	P	—	—
16	P	P	P	—	—
18	—	P	P	—	—
19	—	P	P	—	—
20	—	—	P	—	—
22	P	P	P	—	P
23	—	P	P	—	—
24	—	—	—	—	P
28	P	—	—	—	—
30	P	—	—	—	—
33	P	P	—	—	P
35	—	—	—	—	—
36	P	P	P	—	P
37	P	—	P	—	P
38	P	—	P	—	P
39	P	—	—	—	—
40	P	—	P	—	—
41	P	P	—	—	—
42	P	P	—	—	—
43	P	P	—	—	—
46	—	—	—	—	—
49	—	P	P	—	—
50	—	—	P	—	—
52	P	P	—	—	—
53	—	P	—	—	—
54	P	—	—	—	—
55	—	—	—	—	—
59	—	P	—	—	P
60	—	—	—	—	P
61	P	—	—	—	—
62	—	P	P	—	—
63	P	—	P	—	—
65	—	—	—	—	—
66	—	—	P	N	—
70	—	—	—	—	—
71	—	—	P	—	—
72	P	—	P	—	P
73	—	—	—	N	—
74	P	—	—	—	P
76	—	—	P	N	—
77	—	P	P	—	—
80	—	—	P	—	—
81	—	P	P	—	P
82	—	P	P	—	P
83	—	—	—	—	P
87	—	P	—	—	P
91	—	—	—	N	P
94	P	P	—	—	—
97	—	—	P	—	—
98	P	—	P	—	P
100	—	—	—	—	P

past rather than present trouble as described by Hansel.<sup>9</sup> Waldapfel<sup>20</sup>, in comparing transillumination of the maxillary sinus to x-ray, states that in simple transillumination a difference in darkness of the maxillary sinus can be caused, not only by disease of the sinus, but also by an asymmetry of the two sinuses and varied thickness of the bone. He points out that these physiologic anomalies do not play a part in the x-ray examination and do not influence the results. He further states that

apart from disease of the maxillary sinus itself, darkness in transillumination can be caused, not only by thickness of the bony walls and asymmetry of the maxillary sinus, but also by infiltration of the soft parts, even of the slightest degree. In such instances, he says, the transillumination may show more than the x-ray. He believes complete or massive cloudiness in transillumination with negative x-ray findings is to be regarded as significant of infiltration of the soft parts or subcutaneous edema or hemotoma even if no swelling or discoloration of the skin is evident.

In the forty-five asthma cases without nasal symptoms, eight had an allergic appearing nasal mucosa. In the fifty-five cases with nasal symptoms, both seasonal and perennial, twenty-two had a nasal mucosa suggesting allergy. (Table IV, column 1.) Of the ten patients who had seasonal hay fever with asthma, all had allergic appearing nasal mucosa, as would be expected.

It is interesting to note that the appearance of the nasal mucosa in perennial asthma patients in this series was not markedly different, whether perennial nasal symptoms existed or not.

Transillumination of the sinuses revealed somewhat similar results. Fourteen of the forty-five patients without nasal symptoms revealed positive findings in transilluminating their sinuses, while twenty-three of fifty-five with nasal symptoms were positive.

The sinus x-ray results also disclosed the fact that positive findings were not greatly related to nasal symptoms in asthma. Twenty-seven of forty-five patients without nasal or paranasal symptoms had positive sinus x-rays, while twenty-seven of fifty-five with nasal symptoms had positive plates. (Table IV, column 3).

It would seem from the above that something is transpiring in the nose and sinuses of patients with asthma, whether there are nasal or paranasal symptoms or not. These are probably part of the fundamental pathologic changes that occur in asthma, as suggested by Rackemann<sup>15</sup> and Hansel<sup>8</sup> many years ago.

Grove and Farrior<sup>7</sup>, reporting 200 operative cases of chronic hyperplastic sinusitis in allergic patients, states 165 had asthma, twenty-five hay fever, twelve vasomotor rhinitis, seven urticaria. Blank and Levitt<sup>1</sup> x-rayed the sinuses of 155 patients with perennial rhinitis and 135 showed evidences of pathologic changes mainly evidenced by a thickening of the mucous membranes.

Grove<sup>6</sup> believes disease of the paranasal sinuses is an important focus of infection in asthma. He reports 45 per cent of 470 patients having asthma beginning after ten years of age had sinusitis as the sole cause. Ninety-six per cent of the antra-membranes, removed at operation, showed positive cultures. On the other hand, many allergists, at the present time, feel that the pathology presented by the sinuses in asthma is simulated throughout the respiratory tract, therefore do not see the rational for sinus

## BRONCHIAL ASTHMA—ROSEN

TABLE V  
POSITIVE SKIN TESTS IN 100 ASTHMA PATIENTS

Intracutaneous Tests	Positive Reactors	With Nasal Symptoms	No Nasal Symptoms
Ragweed	40	29	11
Timothy	37	24	13
Dust (1-1000)	19	14	5
Feathers	19	12	7
Tobacco	12	6	6
Horse serum	12	5	7
Orris	11	6	5
Raw silk	11	8	3
Dog ep.	10	7	3
Pyrethrum*	8	7	1
Cotton seed	7	5	2
LePage	6	4	2
Horse ep.	6	4	2
Cat ep.	5	4	1
Kapok	3	2	1
Wool	0	—	—

\*Seven of these eight patients, who were positive to pyrethrum, also had positive skin tests to ragweed as pointed out by Feinberg.<sup>5</sup>

TABLE VI  
POSITIVE FOOD SKIN TESTS IN NINETY ASTHMA PATIENTS

Intracutaneous Tests	Positive Reactors	With Nasal Symptoms	No Nasal Symptoms
Wheat	18	9	9
Milk	15	10	5
Tomato	12	8	4
Egg white	9	5	4
Chicken	6	2	4
Beef	4	3	1

Molds: Only sixty-three patients in this series of 100 were tested for molds. Eight were positive to *Alternaria* and three to *Hormadendrum*.

operation in asthma unless a frank infective state of the sinus itself warrants operation.

## SKIN TESTS (INTRACUTANEOUS)

Lederle extracts in accepted dilutions were used in this series. Dust, tobacco and molds were obtained from the Abbott Laboratories. A wheal of at least 0.5 to 1 cm. was necessary for a slight positive reaction, 1 to 2 cm. for a moderate reaction, 2 + cm. for a marked reaction.

## DISCUSSION OF SKIN TESTS

As would be expected, patients with nasal symptoms revealed more positive reactions than those whose asthma was unaccompanied by any nasal complaints. Only eleven patients were completely negative to all skin tests; seven had only one slight reaction, and eighty-two revealed multiple skin sensitivities of various degrees. As Rackemann<sup>16</sup> states, "When asthma begins before thirty years of age, chances that allergy is the cause is good; after forty-five, asthma is usually intrinsic."

From Table IV, column 4, it can be seen that of the forty-five patients without nasal symptoms seven had completely negative skin tests, while only four of the fifty-five with nasal symptoms were negative. This coincides with Cohen's<sup>2</sup> experience that nasal symptoms appear less frequently in the true intrinsic asthma.

In the eleven skin-test-negative asthmas in the series, findings on examination of the nasal mucosa, x-ray, and transillumination of the sinuses, eosinophila were not particularly different from the group as a whole.

## TOBACCO AND ASTHMA

Ninety-eight of these 100 patients were smokers, averaging about a pack of cigarettes a day or its equivalent in cigars or smoking tobacco. Cessation or tapering off seemed to result in slight improvement of asthma, probably lessening the irritant effect rather than true allergy. There were twelve positive skin tests to tobacco. One of these patients was thought to have a true allergy. He smoked about one pack of cigarettes a day, noted marked improvement on cessation, produced asthma by smoking. The other eleven cases had only slight benefit on avoidance of tobacco.

## BLOOD EOSINOPHILIA

At least three blood smears were taken on each of these hundred asthma patients, usually at weekly intervals. Averaging 5 per cent or over were thirty patients. The highest average count was 16 per cent. Each patient who had eosinophilia received three stool examinations for ova and parasites. They were all negative except in one case where *Necatur Americanus* was found, unaccompanied by gastro-intestinal symptoms (eosinophilia 8 per cent). Schwartz<sup>18</sup> reports an eosinophilia of 5 per cent or over in forty-five of 141 asthma patients of all age groups. Mansman<sup>17</sup> reports eosinophilia over 5 per cent in eighteen of thirty-nine allergy patients.

There was no significant difference in blood eosinophilia between the group of patients who had nasal symptoms and those who did not. Nineteen of the former group of fifty-five had eosinophilia and eleven of the forty-five without nasal symptoms. (See Table IV, column 5)

## NASAL SMEARS—EOSINOPHILIA

These were performed on only forty-six cases in this series, following the technique of Hansel.<sup>9</sup> Each patient had three smears at weekly inter-

vals. Over 15 per cent eosinophile cells on the slide were considered positive. The number of patients was too small to compare with other findings; however, eight cases had at least one positive smear.

*Serology.*—Kahn tests were performed routinely on the 100 patients. All were negative, including three patients who had recurrent attacks of vivax malaria, coincident with their asthma.

*Heart.*—Negative to physical examination in this series. Several patients had EKG examinations with no significant variations from the normal. All had chest plates with no abnormal cardiac findings.

#### X-RAY OF CHEST

This was performed routinely in 100 cases. Eighty-eight were reported normal. The twelve positive findings were as follows (re-rayed at weekly intervals):

- C. N. 3—Slight central thickening and accentuation root branches left lower lobe.
- C. N. 9—Moderate exaggeration bronchovascular markings throughout.
- C. N. 27—Thickened pleura r. costophrenic sinus.
- C. N. 38—Exaggeration bronchovascular markings both bases.
- C. N. 45—Exaggerated bronchovascular and hilar markings, re-ray normal (one week)
- C. N. 63—Coalescing infiltrates r. cardiophrenic angle suggestive of virus pneumonia, re-ray six weeks later normal.
- C. N. 80—Accentuation of lung markings suggestive of pulmonary irritation.
- C. N. 89—Calcified primary tuberculous complexes in parahilar.
- C. N. 92—Productive changes both lower lobes result of previous lipiodol.
- C. N. 93—Slight exaggeration bronchovascular markings.
- C. N. 94—Increased bronchovascular markings.
- C. N. 97—Slight exaggeration lung markings.

There was no significant relationship between x-ray findings of the lungs and blood eosinophilia or nasal and paranasal symptoms and findings.

#### PSYCHOSOMATIC FACTORS IN ASTHMA

These influences are lately receiving much study both from allergists and psychiatrists. In this series of cases as a whole emotional response to illness seemed more likely than, for example, in a group of malaria patients. However, as is true in all organic illness, psychosomatic factors in each asthma patient varied from 1 to 99 per cent.

Not infrequently marked injustice is done to these asthma patients. They are needlessly tagged "psychoneurotics." For example, a patient who had been transferred to this hospital with a diagnosis of asthma and psychoneurosis had a moderate positive skin test to milk. He had never noticed any intolerance to milk, but two weeks on a milk-free diet cleared the "psychoneurotic" symptoms of nervousness, restlessness and tiredness

in addition to the asthma. "Psychoneurosis" and asthma could be reproduced by feeding milk.

On the other hand, another patient was almost completely dominated by mental reaction to his asthma, as evidenced by the fact that a sterile hypo would offer complete relief, though lung findings of asthma persisted.

Six of these 100 asthma patients required neuropsychiatric consultation. Of these, two, although admitted from other hospitals, with additional diagnoses of psychoneuroses, were found entirely normal mentally after allergic treatment had been instituted. The other four received the following diagnosis from the psychiatrist:

- C. N. 3—Mental deficiency, high grade moron.
- C. N. 20—Psychoneurosis, anxiety type, severe, cause undetermined, manifested by tremulousness, fearfulness and uncertainty.
- C. N. 23—Depression, adult maladjustment.
- C. N. 77—Psychoneurosis, anxiety state, moderate, manifested by repressed anxiety, nocturnal smothering attacks, fine tremor of hands and hypersensitivity to noise, cause undetermined.

Hansen-Pruss<sup>10</sup> believes that about 25 per cent of asthmatics suffer from anxiety states which may be primary or secondary to allergic conditions. McDermott and Cobb<sup>13</sup>, in their report of fifty unselected cases of bronchial asthma, report thirty-seven to have some emotional component in the production of their asthmatic attacks.

It seems, from reviewing the literature, that much further study is warranted in the field of psychosomatic allergy. In the words of Eyerman<sup>4</sup>, "It seems that those interested in allergy pay too little attention to the psyche and those interested in the psychic conditioning of bronchial asthma are not aware of the possible allergic explanation for the vagaries of this disease."

*Migraine.*—There were no cases of migraine in this series of 100 asthma patients.

#### ASSOCIATED ALLERGIC SKIN DISEASE

Three patients had atopic dermatitis, two severe, one mild. One patient had frequent severe hives.

#### DRUG ALLERGY

One patient had asthma due to allergy to aspirin. Severe asthma could be produced within two hours after taking five grains. His allergy and ear, nose and throat work-up were entirely negative. Prickman and Buchstein<sup>14</sup> and Feinberg<sup>5</sup> state that skin tests are nearly always negative in aspirin allergy.

#### PHYSICAL ALLERGY

No pure case of asthma due to physical allergy was present in this series. Many patients had adverse or beneficial effects on their asthma with change of heat, cold or other physical factors.

## BRONCHIAL ASTHMA—ROSEN

### RELATIONSHIP OF ASTHMA TO OTHER DISEASES

In this series of 100 asthma patients there was no particular correlation with other non-allergic disease. The following diagnoses also existed at the time of their hospital stay:

- C. N. 13—Small osteoma right frontal sinus.
- C. N. 57—Recurrent vivax malaria.
- C. N. 58—Recurrent vivax malaria.
- C. N. 98—Recurrent vivax malaria.
- C. N. 17—Mild non-suppurative otitis media.
- C. N. 51—Mild non-suppurative otitis media.
- C. N. 46—Defective hearing.
- C. N. 60—Defective hearing.
- C. N. 69—Acute appendicitis.
- C. N. 71—Mild chronic asthmatic bronchitis.

### SUMMARY

1. One hundred consecutive patients with asthma hospitalized in an Army General Hospital were observed with special reference to nasal and paranasal symptoms and findings.

2. Forty-five patients had no nasal symptoms other than an infrequent "cold" in their past history. Fifty-five had either perennial or seasonal nasal symptoms.

3. Of ten patients with seasonal hay fever and asthma, eight had hay fever one to thirteen years before developing asthma; two had the onset of asthma and hay fever together.

4. Of fifteen patients with perennial asthma and seasonal hay fever, nine had their first attack of seasonal hay fever and perennial asthma during the same year; in two the asthma preceded the hay fever by several years; in four the hay fever preceded the asthma by many years.

5. In thirty patients with perennial asthma and perennial nasal symptoms, fourteen date the onset of both concomitantly; nine had their asthma many years before nasal symptoms; in seven the nasal symptoms appeared years before the asthma.

6. Examination of nasal mucosa by an ear, nose and throat consultant performed in each case revealed positive allergic findings in eight of the forty-five patients without nasal symptoms, in twenty-two of the fifty-five with nasal symptoms (including ten with seasonal hay fever).

7. Transillumination of sinuses performed on 100 patients was positive in fourteen of forty-five without nasal symptoms and in twenty-three of fifty-five with nasal symptoms.

8. X-ray of sinuses performed on 100 patients was positive in twenty-seven of forty-five patients without nasal or paranasal symptoms, and in twenty-seven of fifty-five with nasal symptoms.

9. Positive intracutaneous skin tests were more frequent in patients with nasal symptoms, especially with the pollens. Eleven patients negative to all skin tests had less nasal symptoms than the group as a whole.

10. Thirty of these 100 patients had a blood eosinophilia of 5 per cent or over.

## CONCLUSIONS

1. In the two groups of asthma patients with and without nasal symptoms there were no marked differences in nasal mucosa findings (with exception of seasonal hay fever), transillumination of sinuses, x-ray of sinuses and blood eosinophilia. Positive skin tests were much more frequent in the group with nasal symptoms.

2. In perennial asthma nasal symptoms, when present, for the most part occur at or about the same time as the asthma. If not, they may precede or follow the asthma by many years.

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# INFLUENCE OF THE LIVER IN ANAPHYLACTIC SHOCK

## An Experimental Study

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ANALYSIS of the anaphylactic reaction in the dog began with the work of Richet in 1906. In the last few years good reviews of the subject have been published by Dragstedt<sup>3</sup> and Code.<sup>4</sup> In this paper an attempt has been made to consider the problems concerned with the influence of the liver on anaphylactic shock in the dog.

### THE LIVER IN ANAPHYLACTIC SHOCK IN THE DOG

The recognition of the important role of the liver in the phenomenon of anaphylaxis in the dog dates from the observations of Manwaring.<sup>18</sup> This author called attention to the presence of hemorrhagic lesions in the digestive canal, especially in the duodenum, and congestion and subcapsular hemorrhage in the liver. As a result of these observations he decided to study anaphylactic shock in dogs in which the liver had been excluded from the circulation. In five of these animals he was unable to produce anaphylactic shock, but in two animals a mild shock was produced. Manwaring proposed the hypothesis that liberation of a pharmacologically active substance from the liver is the principal factor in anaphylactic shock in the dog, but also that there is a secondary factor dependent on the other organs.

In further investigations Manwaring and his associates<sup>20</sup> showed that the typical response of certain smooth muscle structures, such as the uterus, the urinary bladder and the intestines, did not take place following the intravenous injection of specific foreign proteins into a sensitized dog in which the liver had been excluded from the circulation. From these experiments they drew the conclusion that the characteristic contraction of these structures is due to the sudden formation or liberation by the sensitized liver of chemical products having a histamine-like action.

These results were apparently confirmed by Manwaring and his associates<sup>21</sup> in other experiments. They transplanted the liver of sensitized dogs into normal dogs and then tested the recipient dog with the intravenous specific antigen. A typical fall of arterial blood pressure and contraction of the urinary bladder and intestines invariably occurred in these animals. In addition, loss of coagulability of blood was frequently noticed. They concluded that these experiments furnished conclusive evidence of the hepatic origin of the circulating toxic elements responsible for the characteristic contractions of smooth muscle that occurred during the

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anaphylactic shock. Whether these toxic substances are also responsible for the characteristic fall of arterial blood pressure is not clearly shown from these experiments, because of the mechanical factors introduced by the characteristic engorgement of the transplanted sensitized liver. At the same time Manwaring observed that carotid blood taken from two to five minutes after anaphylactic shock had been produced did not cause a noticeable fall of blood pressure when injected into normal dogs. Nevertheless, in his experiments the blood from the liver did possess definite depressor properties.

The importance of the liver in anaphylactic shock in the dog was also emphasized by the studies of Voegtlin and Bernheim,<sup>30</sup> who never observed the slightest fall of blood pressure when the liver was excluded from the general circulation by an Eck fistula and ligation of the hepatic artery. The experiments of Denecke were also in agreement with those of Manwaring and his associates. In the investigations carried out by Weil<sup>33,34</sup> and by Weil and Eggleston,<sup>35</sup> the conclusion was drawn that the symptoms could not be attributed to the presence of toxic substances in the blood. Weil's hypothesis<sup>34</sup> was that the fall of arterial blood pressure was a secondary result of hepatic congestion.

Simonds and Brandes<sup>29</sup> found that anaphylactic shock did not occur in dogs when the antigen was injected while the circulation through the liver was prevented by occlusion of the hepatic veins but that restoration of the circulation through the liver permitted the reaction to develop.

In summary, none of the authors mentioned in previous paragraphs have been able to demonstrate satisfactorily any of the typical symptoms of anaphylaxis in the dog after exclusion of the liver from the circulation. Indeed, because of the lack of success and the evidence of involvement of the liver in the intact animal, it has been almost universally agreed that typical anaphylactic shock is not possible in the absence of the liver. However, Waters and Markowitz<sup>31</sup> have reported that anaphylactic shock can be elicited in sensitized dogs from which the liver has been completely removed. In four sensitized liverless dogs a pronounced decrease of blood pressure and contraction of the bladder were observed during anaphylactic shock. In the opinion of Waters and Markowitz the production of an anaphylatoxin by the liver is not necessary for the contraction of smooth muscles observed during anaphylactic shock of the dog; the hepatic changes might be only a contributing factor to the fall of blood pressure.

Because of the striking similarity to anaphylactic shock of the results obtained by injection of parasitic extracts it was hoped that a study of one reaction might contribute to the clarification of the other. The intravenous injection of hydatid fluid as well as of the extracts of *Ascaris suum* produced in the dog a shock<sup>13,16,24,25</sup> similar in all aspects to anaphylactic shock. For this reason Rocha e Silva and I<sup>25</sup> considered the shock produced in this manner to be an anaphylaxis-like reaction. Particularly the intravenous injection of these substances produced a marked fall of arterial

blood pressure, decrease of coagulability of blood, thrombocytopenia, leukopenia and marked engorgement of the liver. If the animal recovered from this shock, in general, the reinjection of the same dose or double the dose was ineffective (tachyphylaxis). In this shock produced by parasitic extracts usually the liver liberated histamine; in most of the dogs, during *Ascaris* shock, a definite increase of blood histamine was found.<sup>25</sup>

Mann, Essex and I<sup>15</sup> have made further studies on the influence of the liver in the hypotension produced by injections of the extracts of certain parasites. In the liverless dog there was little or no fall of blood pressure when the animal was injected with a purified extract of *Ascaris* or with hydatid fluid. A similar injection produced a marked fall of blood pressure and usually death in normal dogs. The liverless dogs injected with a crude extract of *Ascaris* showed a mild shock from which they invariably recovered. The conclusion drawn from this investigation was that the liver has an important influence in the production of the fall of blood pressure in the shock produced by injecting extracts of these parasites; however, it must be recognized that other organs may also take part in the reaction.

#### THE LIVER HISTAMINE IN ANAPHYLACTIC SHOCK IN THE DOG

The investigators who found that the liver is responsible for the fall of arterial blood pressure in anaphylaxis in the dog offered different hypotheses for the mechanism of the reaction. Manwaring,<sup>18,19</sup> from his experimental investigations, arrived at the conclusion that the fall of blood pressure is due to liberation of a toxic substance (anaphylatoxin) from the liver and intestines. This was a restatement of the hypothesis of Biedl and Kraus,<sup>1</sup> who thought that the fall of blood pressure in anaphylactic shock in the dog is due to vasomotor paralysis caused by the formation of a toxic peptone-like substance. Weil<sup>33</sup> thought that the hypotension is due to edema and congestion of the liver, for he was unable to detect in recipient dogs any toxic substance in the arterial blood taken from dogs during anaphylactic shock. The amount of blood transfused in each of these experiments ranged from 100 to 600 c.c., the average being 312 c.c. However, in the experiments of Manwaring the blood from the liver did possess definite hypotensive properties.

In the hypothesis of Simonds<sup>28</sup> it is supposed that an obstruction of blood flow due to spasm of the hepatic veins is the underlying factor responsible for anaphylactic shock in dogs. Simonds based his hypothesis partly on the histologic examination of the hepatic veins of the dog because he found that they possess a relatively enormous amount of smooth muscle.

In 1929 Dale<sup>5</sup> supported the hypothesis of an anaphylatoxin; he considered the similarity of the symptoms of histamine injections and anaphylactic shock to be adequate for the recognition of the anaphylatoxin as histamine. Concerning the problem of the role of the liver in anaphylaxis, Dale said:

## ANAPHYLACTIC SHOCK—GRANA

"As Manwaring first showed, and others have abundantly confirmed, the sensitization of the dog to the antigen is almost limited to the cells of the liver. If this organ is completely excluded from the circulation, injection of the antigen into the blood stream has little or no effect. . . . In the dog, therefore, the specific anaphylactic sensitization by antibody chiefly affects the liver cells; when these are injured, by the immune reaction occurring in their protoplasm, histamine, which we know them to contain, is released in such quantities as to produce its effects not only on the liver-vessels but on the histamine-sensitive cells of the body at large."

In 1932 Dragstedt and Gebauer-Fuelnegg<sup>9,14</sup> examined the lymph of anaphylactic dogs and found that a smooth muscle stimulating agent, which was not present normally, appeared rapidly as shock developed. Through further investigations they thought that this substance was histamine. Dragstedt and Mead<sup>10</sup> examined a large number of dogs during the course of anaphylactic shock; testing the blood in the cat, they found histamine activity in the blood regularly whenever an appreciable anaphylactic reaction had occurred. In 1939, Code,<sup>3</sup> using a modification of the method of Barsoum and Gaddum for assaying blood histamine, demonstrated the liberation of histamine during anaphylaxis in dogs whenever the typical signs of anaphylactic shock developed. The concentration of histamine in the blood was increased from two to more than eighty times. Ojers, Holmes and Dragstedt<sup>22</sup> have shown that liver histamine is abruptly decreased in the anaphylactic reaction of the dog; this decrease paralleled the severity of the reaction.

Rocha e Silva and I<sup>25</sup> found that the liberation of histamine from the liver of an anaphylactic dog did not seem to be due to an antigen-antibody reaction, for the perfusion of the liver with horse serum, to which the dog was sensitized, did not produce liberation of histamine. However, during shock in the intact animal the concentration of histamine in the blood increased and the liver lost histamine. The same happened in the shock produced by hydatid fluid and *Ascaris* extract. In dogs, during the shock produced by the intravenous administration of hydatid fluid, there was no apparent relationship between the concentration of histamine in the blood and the degree of fall of carotid blood pressure. In some cases there was a decrease, in some an early increase, and in others a late increase of the concentration of histamine in the blood. The decrease of the concentration of histamine in the liver that was verified in several cases did not show any relationship to the severity of the shock. Experiments on the perfusion of the liver and lungs of dogs with hydatid fluid showed that the fluid was not capable of liberating histamine from the tissues of dogs.<sup>24</sup> In most of the dogs during the shock produced by the intravenous administration of *Ascaris* extract a great increase of blood histamine was produced and the intact liver lost histamine. But the perfusion of isolated livers with Tyrode's solution or defibrinated blood, to which *Ascaris* extract had been added, did not produce liberation of histamine.<sup>25</sup> On the other hand, in our experiments in 5 per cent of the dogs no increase

of blood histamine was observed during *Ascaris* shock, in spite of the fact that the shock was deep and the animals died.

Rocha e Silva and I<sup>25</sup> also found that intravenous injections of liver glycogen in appropriate doses just before the injection of *Ascaris* extract prevented the increase of coagulation time and the increase of histamine content of the blood in *Ascaris* shock. As the injection of glycogen produced severe leukopenia and thrombocytopenia it was concluded that perhaps the accumulation of leukocytes and platelets in the liver plays an important role in the liberation of histamine and heparin.

In the dog we found a striking difference in reaction of perfused organs from that which was observed in the organs of the guinea pig. In the latter, *Ascaris* extract produced an anaphylaxis-like shock in the intact animal and, when the isolated lung of the animal was perfused with this extract, a very large amount of histamine appeared in the perfusion fluid. Consequently the decrease of the concentration of histamine in the liver, as observed in experiments *in vivo* in anaphylactic or *Ascaris* and hydatid-fluid shock in the dog, might be the result of the shock, rather than its cause. The bad nutrition of hepatic cells following the fall of blood pressure and the deep congestion of the liver might account for some injury to hepatic tissue and consequent release of histamine in the blood.

In the last few years a large number of investigations have been made concerning the importance of changes of hepatic function during hemorrhagic shock in rats. These changes, reviewed by Darrow and Engel,<sup>6</sup> consisted of a rise of plasma amino acids,<sup>12</sup> a rise of blood lactate and pyruvate,<sup>26</sup> a fall of hepatic glycogen and a decreased ability to synthesize glycogen from glucose.<sup>17</sup> There were also a fall of the oxygen consumption of liver slices,<sup>27</sup> a decrease of the ability of liver slices from shocked rats to deaminate amino acids and synthesize urea from dl-alanine and ammonium lactate *in vitro*,<sup>36</sup> and modification of the water and electrolyte content of the liver.<sup>6</sup> All these authors have interpreted these findings as indications that the liver is peculiarly subject to anoxia owing to its dependence on portal blood for a large part of its oxygen. Also in the anaphylactic shock of the dog, O'Neill, Moy and Manwaring<sup>23</sup> found that glycogen disappears almost quantitatively from the liver during the first fifteen minutes of the shock.

#### HEPARIN IN THE ANAPHYLACTIC SHOCK OF THE DOG

A striking increase of the coagulation time of the blood occurs during anaphylactic shock in the dog; Eagle, Johnston and Ravdin<sup>11</sup> demonstrated that this noncoagulability is due to a very marked increase in the antithrombic activity of the plasma. Waters, Markowitz and Jaques<sup>32</sup> investigated the changes in the coagulability of the blood of dogs during anaphylaxis and also in peptone shock. In their researches they made use of the observation of Chargaff and Olson<sup>2</sup> that protamine combines quantitatively with heparin *in vitro*. In these experiments they found that the

## ANAPHYLACTIC SHOCK—GRAÑA

anticoagulant in anaphylaxis or peptone shock was completely inhibited by protamine. The role of the liver in the liberation of the anticoagulant in anaphylaxis of the dog had been studied by Weil and Eggleston.<sup>35</sup> They demonstrated that if antigen is added to the blood of a sensitized or normal dog, which then is perfused through a sensitized liver, the blood becomes incoagulable. These experiments demonstrated the participation of the liver but did not necessarily exclude the other organs from a possible share in this process. But in 1938 Waters, Markowitz and Jaques<sup>32</sup> found that in liverless dogs there was no increase of blood heparin when anaphylactic shock was produced.

### CONCLUSIONS

Concerning the influence of the liver in anaphylactic shock and shock produced by injection of certain parasitic extracts into the dog, for the present the following conclusions may be tentatively drawn:

1. The liver is the most important organ in the production of the symptoms of anaphylactic shock in the dog. It is largely responsible for the fall of blood pressure; however, other organs may also take part in this reaction, since a variable degree of fall of blood pressure has been reported in the sensitized liverless dog following the injection of the antigen.
2. The liver of the dog appears to be responsible chiefly for the liberation of heparin; perhaps it is also equally responsible for the increase of blood histamine, since the liver loses large amounts of this substance during the shock.
3. By an unknown mechanism the histamine is liberated from the intact liver during the shock, but not when the isolated liver is perfused with the antigen.
4. All of the foregoing conclusions regarding anaphylactic shock may be drawn from experiments done on dogs in which shock has been produced by injection of certain parasitic extracts.

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# MANGO DERMATITIS AND ITS RELATIONSHIP TO POISON IVY HYPERSENSITIVITY

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THE fruit of the *Mangifera indica* (Mango) is used as a food by one-fifth of the inhabitants of the world and is becoming more important in the United States and England.<sup>20</sup> This large tree, which is a member of the Anacardiaceae and therefore related to the poison ivy plant, is a native of the Indo-Malayan region and has been transplanted to numerous tropical and subtropical countries, such as Brazil, Panama, Hawaii, Mexico, Australia, the Philippines and so forth. It is now widely cultivated in certain parts of Florida and southern California and is being consumed with increasing frequency in New York City.

The fruit, often called the "apple of the tropics," resembles a pear in shape. It is somewhat larger than an avocado. The surface is colored greenish when unripe and a mixture of yellow-orange and red when ripe. The peel is smooth and relatively thin. The fruit contains one large central pit. When ripe, the pulp is soft, stringy and colored orange. It is important to note that the external surface of the peel often shows irregularly distributed deposits of a shiny varnishlike material. This material is contaminating sap derived from the torn stem from which the fruit is suspended. In detaching the fruit from the stem, a small amount of stem sap flows out and may contaminate fruit and leaves.

Cases of Mango dermatitis have been reported as occurring in India<sup>4</sup>, Hawaii<sup>18</sup>, Panama<sup>1</sup>, Peru<sup>17</sup>, Mexico<sup>7</sup>, and, in the United States, in Florida, the Midwest and New York City.<sup>3,14,22</sup> Whereas only a few instances have been reported in the United States, it is probable that this represents only a fraction of the actual incidence. Thus, in this case which we are recording, the diagnosis was entirely overlooked in the first attack. The problem of Mango dermatitis is likely to become more important owing to the increasing consumption of the fruit. More important, however, is the relation of Mango dermatitis to hypersensitiveness to poison ivy and related plants. This relationship has been mentioned before in vague terms, but we propose to define it more precisely on the basis of experimental studies.

The clinical features of Mango dermatitis are similar to those of contact dermatitis based on hypersensitiveness. In general, the intensity and distribution of the rash is a function of the manner in which the fruit is handled, whether by the consumer or those who pick the produce, other factors being constant. In the case of the consumer the eruption

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is apt to be milder, although there is considerable variation from case to case. In these instances the dermatitis, which is acutely erythematovesicular with more or less swelling, affects predominantly the perioral region and the lips, the surrounding parts of the face and sometimes the hands. Those who pick the fruit or who both pick and eat the fruit, as in the cases reported by Simmons and Bolin<sup>18</sup>, are likely to have more extensive rashes with lesions on the fingers, dorsa of the hands, forearms, genitalia and other parts, depending on the nature of the contact. The intensity of the lesions may be such that bullae are formed. Swelling of the eyelids is apt to occur in these patients. The resemblance to poison ivy dermatitis may therefore be considerable. Among those who eat the fruit, stomatitis is occasionally observed.<sup>14</sup> The clinical features, course, and pathogenesis of Mango dermatitis are essentially the same as in poison ivy dermatitis. While there are no features which absolutely differentiate these two forms of dermatitis, that due to Mango is characterized, in those who eat the fruit, by the predominant involvement of the lips and surrounding parts and, particularly, by the absence of definite linear arrangement of vesicles.

The most extensive study of Mango dermatitis is that published by Simmons and Bolin.<sup>18</sup> These observers found that the irritant occurs in the thin viscous sap in the large ducts coursing through the stems attached to the fruit. They recorded thirteen examples of this dermatitis seen in Hawaii. We wish to point out that their group of cases is especially interesting because a large percentage concerned persons who had previously resided in the United States. When these thirteen cases are analysed, it is found that seven had had a known previous history of sensitivity to poison ivy or poison oak. In an additional instance, that of a Japanese, the dermatitis appeared only two days after exposure to the Mango, and it seems probable that this patient had been previously sensitive to Japan lac (*Rhus vernicifera*). In still another instance, there was a previous history of dermatitis from contact with the Mango in Panama. In analysing these data, one point stands out prominently: in all the cases recorded in detail by Simmons and Bolin, the attacks of Mango dermatitis occurred from one to three days after exposure to the fruit. The short reaction period supports the belief that these patients had been previously sensitized by some member of the Anacardiaceae family; and in seven cases, as mentioned, a definite history substantiating this point was actually recorded.

This general concept is further supported by Kirby-Smith's data.<sup>14</sup> He recorded this dermatitis as occurring in from six to twenty-four hours after exposure to the plant. Several physicians who wrote to him expressed the opinion that those susceptible to poison ivy dermatitis were also vulnerable to Mango irritation. Brown and Brown<sup>3</sup> recorded an instance in New York City, in which the patient was seen in a second attack of Mango dermatitis. The history in this case showed that this

patient had previously been afflicted with severe poison ivy dermatitis. Zakon<sup>22</sup> reported two cases in which the dermatitis appeared one day after eating the fruit, but he failed to give any data on the past history of these patients with respect to poison ivy hypersensitiveness.

Patch test studies have hitherto yielded data that at first sight seem to be inconsistent. Brown and Brown<sup>3</sup> and Zakon<sup>22</sup> found that patch tests with the peel of the fruit elicited positive reactions, whereas the juice of the pulp gave negative responses. In addition, Brown and Brown extracted the peels of six Mangoes with anhydrous ether and isolated a yellow waxy-like oil. Patch tests with this oil produced vesicular reactions in their patient and negative results in seven control subjects. No data were furnished in respect to the past occurrence of poison ivy hypersensitiveness in these seven control subjects.<sup>2</sup> Simmons and Bolin<sup>18</sup>, on the basis of extensive experiments, concluded that the only irritant was in the stem sap and that no irritants were present in the fruit and its peel. They stressed the point that the peel could be easily contaminated by the sap issuing from torn stems. It follows, therefore, that a positive patch test to the external surface of the peel may be caused by such contamination, and hence the value of previous patch test data based on the peel of the mango is diminished. It is generally agreed, however, that persons sensitive to the Mango fruit can eat the fruit with impunity provided the peel is removed by another person. Our studies were undertaken to resolve these differences in opinion, if possible.

#### CASE REPORTS

A thirteen-year-old girl of Porto Rican extraction but born in the United States, came to the hospital May 29, 1945, complaining of an eruption about the mouth, the lesions having been present for three days.

Physical examination revealed an erythematous-vesicular eruption on the lips with perioral extension. The lesions were most conspicuous on the upper lip where individual, slightly inflamed vesicles could be discerned. Especially striking was a broad band of superficial inflammation extending from the lower lip down the chin (Fig. 1). There was no evidence of stomatitis.

The only significant point in the past history was that she had had a similar attack of dermatitis in the spring of 1944. This rash, the nature of which had not been recognized by several physicians, lasted until July, 1944, when she went to a camp. There the rash disappeared but during her stay she contracted poison ivy dermatitis.

There was a family history of seasonal asthma and infantile eczema on the father's side. Both parents had eaten Mango fruit for many years with impunity.

In view of the association of poison ivy dermatitis and a perioral dermatitis in a girl of Porto Rican extraction and in view of the inability to implicate any local irritant, such as toothpaste and mouthwash, inquiry was directed toward the possibility of contact with Mango fruit. It was learned that just before the outbreak of the rash, the patient had sucked this fruit in such manner that juice and any contaminants on the fruit moistened the chin and surrounding parts. This had been the first contact with Mango fruit during 1945. The diagnosis of Mango

## MANGO DERMATITIS—KEIL, ET AL.

fruit dermatitis was further supported by the occurrence of a similar eruption in 1944 during the *Mango season*, the disappearance of the rash when she no longer had contact with the Mango fruit in camp, and the association with poison ivy



Fig. 1. Eruption on the vermillion border of the lips and periorally. Note the swelling of the left eye. The lower arrow points to the lesions extending from the lower lip to the chin due to sucking of the fruit.

dermatitis.<sup>8</sup> The patient had eaten Mango fruit many years before without any untoward effect until the first attack in the spring of 1944.

The results of patch tests on this patient are given in Table I. These tests were applied to the forearms, and it is interesting that positive reactions were easily observed even though the skin of the patient was fairly dark in hue. We used 3-n-pentadecyl catechol in concentrations of 0.1 and 1.0 per cent as a standard method of detecting degrees of hypersensitiveness to poison ivy.<sup>10,13</sup> It can be

# MANGO DERMATITIS—KEIL, ET AL.

TABLE I. REACTIONS IN PATIENT WITH MANGO DERMATITIS

Material Tested	Reactions read in		Date of Tests (1945)
	48 hrs.	72 hrs.	
3-pentadecyl catechol in isoamyl acetate 1.0 per cent	1-2 plus	3-4 plus	May 31—June 2-3
0.1 per cent	1 plus	1-2 plus	May 29—June 1-2
0.01 per cent	neg.	neg.	May 29—June 1-2
0.001 per cent	neg.	neg.	May 29—June 1-2
External surface of Mango peel with stem sap contamination	1-2 plus	3 plus	May 31—June 2-3
External surface of Mango peel with no apparent contamination	neg.	2 plus	May 31—June 2-3
Internal surface of Mango peel	3 plus	3 plus	May 31—June 2-3
Mango fruit juice (probably contaminated with knife)	neg.	1-2 plus	May 31—June 2-3
Mango stem sap	2-3 plus	3 plus	May 31—June 2-3
Mango stem sap 1 per cent in isoamyl acetate	1 plus	2-3 plus	May 31—June 2-3
Mango fruit juice (second test)	neg.	plus-minus	June 5-7-8
Internal surface of Mango peel (second test)	2 plus	2 plus	June 5-7-8
Internal surface of Mango peel (third test)	3 plus	3 plus	June 14-16-17
Fleshy fruit adjacent to inner surface of Mango peel	3 plus	2-3 plus	June 14-16-17

seen from the table that the patient was sensitive to certain portions of the Mango fruit and also to poison ivy (positive responses to 3-u-pentadecyl catechol). In order to evaluate these data further, we made detailed studies of the cutaneous reactions to selected portions of the Mango fruit using thirty-nine persons. These data will be discussed in the next section of this article.

On being advised to avoid contact with Mango fruit, the patient showed rapid recovery within the next ten days. This recovery was interrupted early in its course by the supervention of an intercurrent mild edema and itching of the skin about the left eye (Fig. 1), which was attributed either to contamination of the fingers with materials used in the patch tests or a focal reaction to the patch tests. The patient has since remained well since contact with Mango fruit has been avoided.

## CONTROL STUDIES

In view of the paucity of information on the cutaneous effects of the Mango fruit, we applied patch tests with various parts of this fruit to thirty-nine control subjects. In this group six persons had ages ranging from eight to sixteen years, whereas the majority of the remainder were persons in the third and fourth decades. The oldest person tested was sixty-one years old. This was a selected group of people, chosen for the purpose of obtaining a high percentage of subjects sensitive to poison ivy and included nine persons who were seen in an attack of poison ivy dermatitis in various stages of evolution. With the exception of a few instances, the remaining subjects in this control group had had no prior contact with Mango fruit and many were not even acquainted with the fruit.

The patch tests were made in the usual manner. In practically all persons the upper part of the back was used. Reactions were read in

forty-eight and ninety-six hours and graded according to criteria described in another publication.<sup>10</sup> 3-n-pentadecyl catechol in concentrations of 0.1 and 1.0 per cent was used as a standard agent for determining hypersensitiveness to poison ivy.<sup>10,13</sup> The Mango fruit tested was the specimen which our patient with Mango dermatitis brought in. The surface of the fruit was obviously contaminated by stem juice. Towards the end of the study another Mango fruit was used, which seemed to be uncontaminated by stem sap. Through the kindness of Mr. T. H. Everett of the Bronx Botanical Gardens, we received a quantity of Mango stem sap which had been collected in Florida with considerable difficulty during November, 1944. This material was an odorless, translucent, sticky mass of dull white color with a pinkish overcast. It was kept in a sealed vial at approximately 4°C. in a refrigerator until used for these studies. The only change observed in our specimen during the course of our study was a gradual and slight darkening to a pink brown color.

Among the group of thirty-nine persons, twenty-five were found to be hypersensitive to 3-n-pentadecyl catechol (Table II), whereas the remaining fourteen subjects gave completely negative responses to this substance in concentrations up to 1 per cent. The group of twenty-five persons sensitive to 3-n-pentadecyl catechol included, as was to be expected, the nine persons who were seen in an attack of poison ivy dermatitis.

(1.) *Negative Reactors to 3-n-pentadecyl catechol.*—Among the fourteen persons who gave negative reactions to 3-n-pentadecyl catechol, all likewise showed negative reactions to the internal surface of the peel and the fruit juice. In this group of fourteen, nine patients who were patch-tested with Mango stem sap and a 1 per cent dilution of this sap, all showed negative responses. These results indicated, therefore, that the various portions of this plant, including our specimen of stem sap, were not primarily irritating to the skin. This finding does not preclude the possibility, however, that the pure ingredients, when isolated, may prove to be primarily irritating as such.

(2.) *Positive Reactors to 3-n-pentadecyl catechol.*—Analysis of the twenty-five cases in this group revealed the following information (Table II):

(1) *Mango fruit juice.*—Juice taken from the pulp was patch-tested in twenty-four subjects, with essentially negative reaction in all.

(2) *Internal surface of the Mango peel.*—Among twenty-four persons patch tested with the internal surface of the peel, only six (Cases 3, 4, 7, 9, 22, 25) showed positive responses ranging from 1 plus to 2-3 plus. Four of these reactions were observed in cases exhibiting an attack of

TABLE II

Case	Past History of Poison Ivy Dermatitis N = No Y = Yes	3-Pentadecyl Catechol in Isoamyl Acetate		Mango Peel Fruit Surface (Internal Surface)	Mango Pulp Juice	Mango Stem Sap		Mango Stem Sap 1% in Isoamyl Acetate	Clinical Diagnosis
		0.1%	1.0%						
1	N		neg.	neg.	neg.	neg.			Eczema upper eyelids; cause not determined.
2	Y	neg.*	++(+)			+(+)	neg.	neg.	Mild poison ivy dermatitis.
3	N	+	+++	±	neg.	++(+)	+	++	Tinea cruris. See text for additional data.
4	Y	++++(+)	++++(+)	++(+)	±	++		++(+)	Acute poison ivy. See text for additional data.
5	N		+++	neg.	neg.				Nummular eczema
6	Y	+	+++	neg.	neg.	+	+	+	Acute poison ivy
7	Y	++(+)		++(+)	neg.				Allergic to quinolor ungt.
8	N		++	±	neg.	neg.	+	neg.	Atopic dermatitis
9	Y	+	++	+	neg.	++(+)	++(+)	++	Poison ivy dermatitis
10	N		++	neg.	neg.	neg.	neg.	neg.	Atopic dermatitis. Atc mangos many years ago
11	N		++	neg.	neg.	+	+	neg.	Dermatitis venenata probably due to Mazon
12	N		++(+)	neg.	neg.	neg.	neg.	neg.	Neurodermatitis of the neck

MANGO DERMATITIS—KEIL, ET AL.

13	Y	neg.	neg.	neg.	++	neg.	++	neg.	neg.	neg.	neg.	neg.	neg.	neg.	Subacute eczema of the hands. Occupational?
14	Y	±	+	++	+++	neg.	+++	neg.	neg.	neg.	±	++	neg.	+	Nail polish dermatitis. See text.
15	Y				++	neg.	++	neg.	neg.	neg.	neg.	neg.	neg.	neg.	Generalized pruritus. See text for delayed reactions.
16	Y	neg.	++	++	++	++	++	neg.	±	neg.	neg.	++	neg.	neg.	Folliculitis of bearded area with secondary contact dermatitis
17	Y	+++	+++	+++				±	neg.	neg.	neg.	+++	+	+	Acute poison ivy dermatitis
18	N				++	+	++	neg.	neg.	neg.	neg.	±	±	neg.	Dermatitis of hands. Weeds? Medicaments?
19	N	neg.	neg.		++	neg.	++	neg.	neg.	neg.	neg.	neg.	neg.	neg.	Contact dermatitis due to ink solvent.
20	Y	+++	++	++				±	neg.	neg.	neg.	++	++		Acute poison ivy dermatitis.
21	Y	neg.	neg.			++	++	neg.	neg.	neg.	neg.	neg.	neg.	neg.	Dermatitis venenata due to ointment.
22	Y	++	++	++				neg.	++	neg.	neg.	++	++	++	Acute poison ivy dermatitis.
23	Y	++	++	++				neg.	neg.	neg.	neg.	+	++	neg.	Bullous eruption due to sun
24	Y	+	++					neg.	neg.	neg.	neg.	++	++	++	Poison ivy dermatitis
25	Y	neg.	++	++				neg.	+	neg.	neg.	++	++	++	Acute poison ivy dermatitis

\*Where for the same case number there are two readings for one set of conditions, the reading on the left was made after forty-eight hours and that on the right after ninety-six hours

poison ivy dermatitis at the time of examination (Cases 4, 9, 22, 25). All six positive reactors were among those showing positive responses to 3-n-pentadecyl catechol in a concentration of 0.1 per cent. However, no absolute correlation could be established between the reactions to the internal surface of the peel and 3-n-pentadecyl catechol. The difficulty in evaluating patch tests with peel of the Mango lies in the frequent contamination of the external surface of the peel with exuding stem sap. Although care was taken in applying the peel with its *internal* surface against the skin, the possibility of contamination cannot be absolutely eliminated. However, in two subjects (Cases 3 and 4) additional patch tests were made with a portion of the fruit adjacent to the peel, and in both instances significant responses were obtained (1-2 plus and 3-4 plus respectively). For these reasons, we feel that, although the possibility of contamination must be considered in evaluating these results, it is likely that the peel contains a small amount of irritant. Whether this is caused by stem sap penetrating the peel or by the presence of an irritant *ab initio* it is difficult to state with certainty in the absence of a chemical examination of uncontaminated peel. If the presence of irritant in the peel is verified, the amount will probably vary with each specimen, depending on many factors, perhaps in a manner similar to the fruit of the poison ivy plant.<sup>10</sup>

(3) *Mango stem sap*.—In twenty-one persons patch-tested with our specimen of Mango stem sap, fourteen gave positive reactions ranging from 1 plus to 3 plus. In seven of the positive reactors to the stem sap (Cases 3, 9, 17, 20, 22, 24, 25), the responses were relatively intense (2-3 plus to 3 plus). The incidence of positive cross-reactions was therefore 66 per cent for the entire group and 33 per cent for those showing intense reactions. It may be noted that all nine patients showing clinical poison ivy dermatitis at the time of observation, also gave positive responses to Mango stem sap.

(4) *1 per cent Mango stem sap*.—This concentration of Mango stem sap was tested in twenty persons. Significant positive reactions were obtained in nine persons. Generally, the intensity of reaction was much less than that elicited by the undiluted Mango stem sap.

(5) *Miscellaneous data*.—In two instances (Cases 14 and 15) interesting immunologic phenomena were encountered.

In Case 14 the site of the internal surface of the peel, which had revealed no alterations on the fourth day, showed a spontaneous flare-up about the tenth day (2-3 plus), according to the history. When seen on the thirteenth day, the sites of 3-n-pentadecyl catechol 0.1 per cent, Mango stem sap and 1 per cent Mango stem sap, all of which had previously given mild positive reactions, now also became more intensely

positive (3 plus; 2-3 plus; and 2-3 plus, respectively). It appeared that the grade of hypersensitiveness had been increasing gradually or that the skin had become sensitized to the internal surface of the peel.

In Case 15 the reactions to Mango stem sap and a 1 per cent dilution of this stem sap were recorded as negative at ninety-six hours, although these patches were really not fully occlusive. When these tests were repeated five days after the initial patches had been applied, both fresh sites showed no reactions at forty-eight hours but two days later they revealed responses graded as 1-2 plus. At this time it was noted that the two initially applied patch tests of Mango stem sap and its 1 per cent dilution showed definite focal reactions graded as 1 plus and the site of the internal surface of the peel also exhibited a milder, although definite, erythema graded as 1 plus. Here, the possibility of artificial sensitization must be considered in view of the temporal relations involved.

It is possible that these cases illustrate the point that persons sensitive to the poison ivy plant are more easily sensitized to the Mango plant. An analogous phenomenon has also been encountered by us in tests made with derivatives of cashew nut shell liquid.<sup>9</sup>

#### DISCUSSION

1. *Relation of Mango Dermatitis to Poison Ivy Hypersensitiveness.*—The data recorded in this paper show that there is a definite relation between Mango dermatitis and hypersensitiveness to poison ivy as indicated by the reactions to 3-n-pentadecyl catechol. This relation is not surprising when it is considered that these plants belong to the same family, the Anacardiaceae.

It has been shown by the patch-test technique that persons who do not react to 3-n-pentadecyl catechol give negative responses to various portions of the Mango fruit, including the stem sap. Among twenty-one persons showing positive responses to 3-n-pentadecyl catechol, the Mango stem sap elicited various degrees of positive reactions in 66 per cent of the cases, whereas in twenty-four persons sensitive to 3-n-pentadecyl catechol the inner surface of the peel gave only 25 per cent cross-reactions. It should be stressed that these group reactions were obtained in many patients who had had *no prior contact* with the Mango fruit. Table 2 also shows that all nine persons who were seen in a clinical attack of poison ivy dermatitis gave positive reactions to Mango stem sap. On the other hand, only four gave mild, though significant, responses to the inner surface of the peel when tested in eight of the nine persons with poison ivy dermatitis. In fourteen patients sensitive to a dilution of 0.1 per cent 3-n-pentadecyl catechol, positive reactions to the stem sap were obtained in all, and, in general, this concentration of 3-n-pentadecyl catechol seemed to be about equivalent to our specimen of Mango stem sap. In the case of patients who failed to react to 0.1 per cent concentra-

tion, the reactions to Mango stem sap were negative. These data appear to show that a fairly high grade of sensitivity to 3-n-pentadecyl catechol (and therefore to poison ivy) is required for eliciting positive responses to Mango stem sap.

There is also a high incidence of antecedent poison ivy dermatitis among those contracting Mango dermatitis. This is shown by the cases reported in the literature.<sup>1,3,14,18</sup> Mr. T. H. Everett of the Bronx Botanical Gardens was afflicted with poison ivy dermatitis many years ago and subsequently had an attack of Mango dermatitis. In the case detailed in this paper, poison ivy dermatitis was apparently contracted after a prior attack of Mango dermatitis.

It appears that persons sensitive to poison ivy are probably apt to become sensitized to Mango fruit on adequate exposure, as seemed to be true in two of the twenty-five cases collected in Table II.

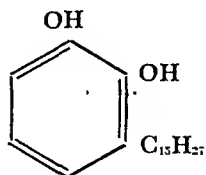
Dermatitis due to Mango fruit and to poison ivy are merely representative of what Merrill<sup>16</sup> called collectively the anacardiaceous dermatitis.\*\*

*2. Irritants in Mango Fruit and Data on Their Probable Chemical Nature.*—Patch test studies have therefore pointed definitely to the occurrence of an irritant or irritants in Mango stem sap, probably also in the peel itself. The evidence implicating the stem sap is, in our opinion, beyond dispute; that for the peel itself is less conclusive. The previous reports on positive patch tests to the peel<sup>3,22</sup> are rendered less significant since apparently no provision was made to eliminate the possibility of contaminating stem sap on the surface of the peel. However, our studies seem to point to the likelihood that the peel itself contains an irritant, probably in small amount.

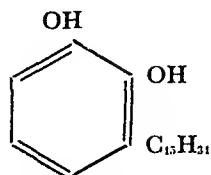
Typical of the noxious ingredients in the Anacardiaceae, to which the poison ivy plant, Japanese lacquer tree, cashew nut tree, marking nut tree and many others belong, are catechol, resorcinol and phenol derivatives with a long unsaturated side-chain in the position meta to at least one hydroxyl group.<sup>11,12</sup> The active irritant in the poison ivy plant is an oily substance called urushiol. Urushiol is known to be a vicinal derivative or mixture of derivatives of pyrocatechol (1, 2-benzenediol) with an unsaturated straight chain of 15 carbon atoms in the number 3 position. The uncertainty in the structure of these compounds lies in lack of knowledge as to the location of the double bonds in the long chain alkyl substituents and the degree of their unsaturation. Urushiol on catalytic hydrogenation absorbs 2 molecules of hydrogen and is converted to a white solid known as tetrahydro urushiol (2-n-pentadecyl catechol). Small amounts of this saturated compound, which was the synthetic compound used by us in this work to detect hypersensitiveness to the poison

\*The data recorded by us<sup>10-12</sup> indicate that the cases of bhilawanol oil dermatitis<sup>5</sup> and of "diholic mark dermatitis"<sup>13</sup> are probably, for the most part, group reactions to related substances occurring in persons already hypersensitive to poison ivy.

ivy plant<sup>10,13</sup>, have also been reported to be present in urushiol. The chemical formulás for these substances are:



poison ivy "urushiol"  
(average representation for this mixture)



3-n-pentadecyl catechol

We have found<sup>11,12</sup> that in persons sensitive to poison ivy the fundamental structural requirement for groups reactivity is the presence of a long unsaturated side-chain in the position meta to an hydroxyl group attached to a benzene ring. Only two references bearing on the chemical nature of the Mango irritant have been noted in the literature, and it is evident that the chemistry of these substances is still in its infancy. Goudswaard<sup>6</sup> claimed that he had isolated from the twigs of a species of *Mangifera* a substance similar to cardol (a resorcinol derivative with an unsaturated side-chain similar to that in poison ivy "urushiol"). Vasistha and Siddiqui<sup>21</sup> examined the sap ("chep") issuing from the stems of the *Mangifera indica* and isolated, among other components, a phenolic compound with molecular formula and properties that seem to be those of a catechol derivative similar to a pentadecyl substituted catechol, but their data are inconclusive for the verification of the precise nature of this substance. In any event, we have reason to feel that, when the nature of the Mango irritant or irritants are definitely identified, these compounds will be found to obey the fundamental rule regarding the position of the side-chain in respect to at least one hydroxyl group. Thus far, no exceptions have been encountered among the Anacardiaceae.

3. *Some Practical Deductions.*—Certain practical conclusions follow from consideration of the data presented.

(a) The fruit can probably be eaten without serious danger of developing dermatitis, provided there is no contact with stem sap and, possibly also, the peel. More study is needed to determine with certainty whether the peel *per se* is irritating and under what circumstances.

(b) Persons with a high degree of sensitivity to poison ivy, as indicated by responses to 3-n-pentadecyl catechol in proper concentrations, should be wary of contact with Mango fruit, whether as consumer, picker or peeler. However, such persons can probably eat the fruit safely when it is peeled by another person.

(c) To diminish the incidence of dermatitis from Mango fruit, methods are needed to prevent contamination of the surface of the peel

with stem sap and to remove such contamination by means of some innocuous solvent or solvents.

(d) This is one of the situations, in our opinion, where a pre-employment patch test, using 3-n-pentadecyl catechol in proper dilutions, may be useful in detecting that portion of the population which is sensitive to the poison ivy and related plants. In New York City and its environs this represents about 35 per cent of the population over eight years of age.<sup>9</sup> No precise data have yet been compiled on the sensitizing ability of the Mango irritant.

#### SUMMARY AND CONCLUSIONS

A case of Mango dermatitis with typical clinical features is reported. This type of dermatitis is likely to be encountered with increasing frequency owing to two factors: (a) increasing consumption of the fruit; (b) the close immunologic relation to hypersensitiveness to poison ivy and related plants.

Experimental studies on thirty-nine control subjects show that the irritant is the stem sap which often contaminates the external surface of the peel. Less conclusive evidence is presented to implicate the peel itself. The pulp and its juice are innocuous.

Our control group comprised thirty-nine subjects who in the vast majority of cases had had no prior contact with Mango fruit. Based on the responses of 3-n-pentadecyl catechol, which was our standard method of detecting hypersensitiveness to poison ivy, the subjects could be classified in two categories: (1) A group including 14 persons who were not sensitive to poison ivy and all showed negative responses to various portions of Mango fruit, including the stem sap. (2) A group comprising twenty-five persons sensitive to poison ivy, of which nine were seen in a clinical attack of poison ivy dermatitis. In this group the following incidence of cross-reactions was obtained: stem sap, 66 per cent of twenty-one persons; internal surface of the peel, 25 per cent of twenty-four persons. When comparisons were made on a quantitative basis, it was found that our specimen of Mango stem sap was about equivalent in its cutaneous effects to 0.1 per cent 3-n-pentadecyl catechol. All subjects who were observed in a clinical attack of poison ivy dermatitis showed positive patch tests to the stem sap, and much less often to the internal surface of the peel. In this group of twenty-five, fourteen reacted to 0.1 per cent 3-n-pentadecyl catechol and all fourteen gave positive reactions to Mango stem sap. In general, those who first reacted at a concentration of 1 per cent 3-n-pentadecyl catechol (and were therefore less sensitive) gave negative responses to the stem sap. These data seem to show that a fairly high grade of sensitivity is requisite for positive patch tests to Mango stem sap. The possibility that persons sensitive to poison ivy are more easily sensitized to the Mango plant was illustrated by two instances in the control group.

Typical of the noxious ingredients in the Anacardiaceae are catechol, resorcinol and phenol derivatives with a long unsaturated side-chain in the position meta to at least one hydroxyl group. Moreover, in persons sensitive to poison ivy, the fundamental structural requirement for group reactivity is the presence of a long unsaturated side-chain in the position meta to an hydroxyl group attached to a benzene ring. It seems probable that this fundamental postulate will be satisfied chemically when the irritants in the Mango stem sap and, possibly also, in the peel are fully characterized.

Some practical suggestions are made in relation to the handling of this fruit by consumer, picker and peeler.

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# SOME CLINICAL OBSERVATIONS ON THE USE OF BENADRYL FOR THE SYMPTOMATIC RELIEF OF ALLERGIC CONDITIONS

A Report of 188 Cases

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UPON the basis of Lewis' theory, that liberation of the H-substance or histamine produces the acute allergic reaction, the chief characteristics of which are smooth muscle spasm and increased capillary permeability—attention has recently been attracted to the use of histamine neutralizing agents. While there are several objections to this theory, it remains as acceptable as any existent, and as time goes on, the primary premise of this theory seems strengthened.

The typical hive is a manifestation of increased capillary permeability and extravasation of the plasma into the tissues. Bronchospasm in the human and anaphylactic shock in sensitized guinea pigs are manifestations of smooth muscle spasm. On the assumption of this theory that the antigen-antibody combination in the sensitized areas causes a liberation of histamine, there is produced the effects seen in an allergic or anaphylactic reaction. The signs and symptoms are analogous to the effects of the injection of the histamine. Since urticaria is visible and easily followed in its course and the induced wheal is one of the most important diagnostic signs of hypersensitivity, this clinical condition is of especial value in estimating symptomatic relief of the acute allergic reaction.

As early as 1918, Dale and Laidlow studied the effect of epinephrin as a histamine antagonist and while some of the acute effects of histamine may be controlled by it, epinephrin had other important side effects. Atropine also has a blocking effect on histamine action but is best known for its inhibiting effect upon the vagus and other parasympathetic nerve endings. It has more of an anti-choline action than an anti-histamine action. Code describes two potent anti-histamine drugs found by Bonet and Staub in 1937. Their toxicity minimized their clinical usefulness. Others also have been described suggesting that more effective anti-histamine agents would appear later.

At this time only brief reference will be made to the use of ethylene disulphonate. It was not proposed by the original investigators or subsequent proponents that this is an anti-histamine substance but that the theoretical action is "in correcting the tissue defect by which a person is permitted to become allergic in the first place" (Shannon). Evans, Bodman and Maisin, in 1940, theorized that the defect was a failure in intracellular metabolism such that carbohydrate oxygenation was incomplete and that in familial allergy there was a primary failure and in acquired allergy some agent destroyed the enzyme necessary for this

chemical change. Since several well-qualified workers have reviewed the use of this substance by actual experience and have co-ordinated it with their past experiences, many allergists have come to the opinion that this substance is no more effective than other forms of non-specific therapy and Archibald "found no justification for the use of ethylene disulphonate in the treatment of children's allergies." Fish, Small and Foard conclude that this agent did not afford a significant degree of protection against anaphylactic shock.

The use of a hapten such as the combination of histamine and horse serum globulin (Sheldon and associates) was hoped to render the treated individual resistant to histamine itself and thus control the allergic reaction. This writer's experience with this hapten was distinctly disappointing and, after a number of urticarial patients, fully though unsuccessfully treated by it, were promptly and completely relieved by one of the histamine neutralizing drugs and which is described below, the use of this agent was discarded entirely.

In 1929 and 1930, Best and McHenry's histaminase offered a suggestion of the possible neutralization of the toxic action of histamine but we are all familiar with the disappointments of the histaminase era. More recently, other anti-histamine drugs which have the property of neutralizing histamine *in vitro* and protecting sensitized animals against anaphylactic shock have been described.

#### BENADRYL

One of these histamine neutralizing substances which has received wide publicity and from which encouraging clinical reports are being offered is that known as benadryl or beta-dimethylaminoethyl benzhydryl ether hydrochloride. This was first reported in 1945 by Loew and associates in work with experimental animals and the first clinical report made shortly thereafter by Curtis and Owens in the treatment of urticaria. We reported on the same subject in October, 1945, and since then several reports have emanated from clinics and presentations have been made at various medical meetings.

Its chief characteristics of importance to the discussion are the alleviation of histamine shock in guinea pigs in which it is described as being fifteen to thirty times more active than aminophyllin, the alleviation of anaphylactic shock in guinea pigs in which it protected more than those treated with aminophyllin, and the antispasmodic *vitro* experiments with guinea pig smooth muscle. With papaverine as an index of the ability to control the contractile response to histamine, acetylcholine and barium chloride, benadryl was reported as being 650 times as active against histamine, 50 times as active against acetylcholine and 1.3 times as active against barium chloride.

While its clinical use has shown the chief side-effects of drowsiness, dizziness, dry-mouth and nervousness in a considerable percentage of

## BENADRYL IN ALLERGIC CONDITIONS—TODD

patients using the drug, the toxicity is very low and no changes in the blood counts, urine and blood chemistry were demonstrable even in those cases using the drug for as long as six months. In our experience with some 200 cases, 188 of which have had an adequate clinical trial on the drug, the side-effects were usually very brief and rarely more than that seen with some of the ephedrin and barbiturate mixtures except in three cases who complained strongly of dizziness and confusion. Our side-effects were minimized by the use of the minimum amount to secure relief. Histopathologic studies by the originators showed no evidence of acute or chronic changes in the viscera.

Effective dosage varies widely in different individuals and clinical conditions. At one clinic, dosage by mouth in the adult ranged from 50 to 500 mg. daily and 20 mg. by intramuscular injection. Intravenous drip of 10 to 120 mg. in a ten-minute period was used with an average of 60 mg. per 100 c.c. of normal saline solution. In childhood, up to age fourteen, the dosage of 2 mg. per pound of body weight was suggested.

In our experience, we were impressed with the rapidity of action and full therapeutic effect of relatively small doses in the acute manifestations and the relatively much smaller dose necessary for maintenance after the first one to three days of treatment. The chronic cases required much more. Our dosage reached an arbitrary level somewhat as follows: 20 to 40 mg. intravenously or intramuscularly plus 200 mg. daily by mouth at the onset of treatment, discontinuing the injections as soon as substantial relief was experienced and reducing the oral administration to 50 mg. daily or every second day as soon as complete relief was experienced. Small maintenance doses either by capsule or elixir by mouth were continued when deemed necessary. Children are easily treated by the elixir made up to contain 5 or 10 mg. per 4 c.c.

### CLINICAL CASES

We have used it in more than 200 cases, with adequate clinical trial in 188; the others being still under observation or are patients not yet returned for check-up. Our results are presented in Table I. We have purposely selected those cases for treatment which theoretically should respond best to histamine neutralization.

With the reported good results from various clinical investigators concerning the acute allergic manifestations such as urticaria and vasomotor rhinitis, our experiences are in close agreement. It is almost universally successful in these acute manifestations but, of course, it does not cure or remove the fundamental etiology. Symptoms in the chronic case recur promptly after the drug is discontinued but usually as promptly disappear again after resumption of the drug.

Williams has found in a study of 362 cases which included Sluder's syndrome, histamine cephalalgia, myalgia of the head, vasomotor rhinitis, hyperplastic sinusitis and Ménière's syndrome that these were so closely

# BENADRYL IN ALLERGIC CONDITIONS—TODD

TABLE I. DEGREE OF SYMPTOMATIC RELIEF OF OUTSTANDING SYMPTOM WITH BENADRYL ADMINISTRATION

CHIEF COMPLAINT RELATED TO	COMPLETE	PARTIAL	NONE	TOTAL PATIENTS
I SKIN				
A. URTICARIA AND EDEMA				
1. Acute to subacute	13			13
2. Chronic; recurrent	42	1		43
3. Whealing reactions from:				25
(a) Penicillin	10			
(b) Sulfonamids	4			
(c) Insecticides	3			
(d) Liver Extract	2			
(e) Horse Serum	1			
(Antitetanic)				
(f) Aspirin	2			
(g) Prostigmin	1			
(h) Allergic Testing	2			
B. ECZEMATOID DERMATITIS, GENERALIZED	6	4	2	12
C. CONTACT DERMATITIS	3	1	1	5
II RESPIRATORY TRACT				98
A. RHINITIS, PERENNIAL (VASOMOTOR)	31	4		35
B. RHINITIS, SEASONAL (POLLEN)	11			11
C. VASOMOTOR LARYNGITIS	2	1		3
D. ASTHMA WITH RHINITIS	2	3	1	6
E. ASTHMA ONLY	4	10	4	18
III GASTRO-INTESTINAL TRACT				73
A. FOOD ALLERGICS WITH PRINCIPAL SYMPTOMS RELATED TO G-I TRACT	6	1		7
IV CENTRAL NERVOUS SYSTEM				
A. MIGRAINE	3		5	8
B. MENIERE'S SYNDROME	2			2
				10
				188

related and with symptoms overlapping that all might well be included under the designation of "Allergy of the Head" because he believed they were due to the same fundamental physiologic mechanism—namely, physical or intrinsic allergy. He was especially impressed with benadryl in relieving the syndrome in those cases in which it was tried, especially as regards the vasomotor rhinitis component.

It is useful, so far as allergic practice is concerned: (1) in those patients exhibiting a generalized non-specific irritability of the skin which is subclinical but becomes manifest when attempting to do the routine skin tests, it very definitely lowers the diffuse histamine concentration of the tissues so that subsequent skin tests are more selective and specific in their significance; (2) in maintaining the urticarial or rhinitis patient in comfort for a few weeks until specific desensitization becomes effective after the fundamental etiology is determined; (3) in controlling occa-

## BENADRYL IN ALLERGIC CONDITIONS—TODD

sional reactions seen after testing in which a number of positive reactions have been obtained and in which an excessive amount of histamine appears to be liberated and which may produce distressing symptoms; and (4) in controlling the many acute but transient allergic manifestations in daily practice in a prompt and convincing way.

It very definitely controls urticaria following liver injections, penicillin by mouth or by injection and urticaria after sulfonamids; it controls urticarial and angioneurotic edema of serum sickness; it relieves both the allergic (antigen-antibody) whealing and the non-allergic whealing reactions in the great majority of cases and does it much more promptly than does adrenalin, requiring less treatment, and the effects of the medication are more persistent and with less side-effects.

With the more chronic allergic conditions such as asthma, chronic eczematoid dermatitis, chronic rhinitis with polypoid degeneration, et cetera, the hopes that this drug might be of equal value have not been fulfilled. While partial relief is obtained in a considerable percentage and a few have been strikingly relieved, there were more who received no demonstrable benefit. In these conditions, the tissue changes may have reached an irreversible stage.

### SUMMARY

There are histamine-neutralizing drugs in production and under clinical investigation which may be of great value and perhaps with no side-effects, but the belief expressed in some quarters that a universal blanket treatment for allergy is imminent is not yet justified. However, from the past experiences with the indiscriminate use of histaminase, we can readily believe that when these histamine-neutralizing agents of greater potency become more widely used, all types of clinical conditions, allergic and others, will be treated with lavish abandon. It is well for the allergist to be prepared to properly evaluate the true relationship of the drug to the conditions being treated. The new agent will be of inestimable value in controlling the acute allergic phenomena that fall in his domain. Some of these conditions such as urticaria and intrinsic rhinitis have always been difficult to handle. In the meantime, it gives an opportunity to work out the fundamental allergic factors with the better opportunity of securing the most lasting results.

A word of caution is obligatory. While no case as yet has come to our notice of acquired allergy to benadryl, one must always remember that, wherever large numbers of hypersensitive individuals are being administered a complex organic drug, it is possible that some may react in an abnormal way and develop a depressant effect upon the hematopoietic system.

Also, as Swineford has pointed out, the term anti-histamine drug is a partial misnomer, since the drug nullifies only part of the pharmacodynamic action of histamine.

# CONCLUSIONS

1. Benadryl was used for symptomatic relief in 188 cases. It was strikingly successful in vasomotor rhinitis, the urticarias and acute whealing reactions to drugs and biologicals and some reactions of testing. In other conditions falling in the allergic domain, it was not as successful.

2. Thus far, no acquired allergy to the drug has been reported but this possibility must be kept in mind. It has some distressing though not insurmountable side-effects.

3. Aside from the short self-limited whealing reactions, it is not curative but is anticipated to be used largely for symptomatic relief while approved allergic management becomes effective.

4. Hypersensitivity is a constitutional condition and the discovery and elimination of allergens and exciting factors still remain the chief task. Symptomatic relief is necessary and desirable but should not overshadow the main function of the allergist.

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## BENADRYL IN THE TREATMENT OF ERYTHEMA EXUDATIVUM MULTIFORME

HERMANN PINKUS, M.D.

Monroe, Michigan

SEVERAL recent publications<sup>1,2,3,4</sup> have called attention to the clinical effects of a new chemical compound which counteracts histamine in experimental animals and is effective in urticaria and other allergic manifestations in human beings. It has been suggested<sup>2,3</sup> that this drug, beta-dimethyl-aminoethyl benzhydryl ether hydrochloride (Benadryl) may be effective in erythema exudativum multiforme, but no case histories have been reported. It may be of interest therefore to report the results obtained in four cases of this type, two patients suffering from typical idiopathic erythema multiforme, the other two from erythemas of toxic origin.

*Case 1.*—R. B., a white man, aged forty-three, was seen on June 16, 1945 with an erythematous bullous eruption on the back of his hands, the forearms, legs, nape of the neck, scalp, ears, and lips. He had been seen with a similar eruption in January, 1942, and gave a history of having been hospitalized for several weeks with a very severe attack fifteen years previously. The lesions which the patient presented in 1942 had responded well to sodium salicylate in doses of ten grains four times daily. His condition had begun to improve within three days, and the eruption had disappeared within ten days.

The patient now had been feeling bad for about a month, his chief complaint being general lassitude, backache, and loss of appetite. He began to break out five days before he consulted me. Early lesions consisted of tense bullae up to pea size. These soon became surrounded with erythematous borders, the center began to form crusts, and typical "herpes iris" lesions resulted. Biopsies from two different lesions on the hands showed the typical histologic changes of bullous erythema multiforme. The patient was given ten grains of sodium salicylate four times daily, but the eruption kept spreading and involved the oral mucosa. He was hospitalized June 18, and salicylates were given by mouth and intravenously to tolerance. This gradually controlled the eruption, and the patient was discharged June 25. He continued taking salicylates by mouth. The lesions cleared slowly, but recurred July 5, a few days after he had discontinued medication. During this period he continued to feel weak and complained of backache and poor appetite. July 6 he was given Benadryl in 50 mg. capsules\*, one capsule twice a day. The eruption began to dry up within twenty-four hours, and only remnants were left by July 11, when he reported feeling fine. Not only had the cutaneous lesions disappeared, but also lassitude, backache, and loss of appetite. The patient then took fifty milligrams three times daily until July 16 in order to prevent relapse.

The patient returned two months later (September 7) with a recurrence of iris lesions on hands and forearms of two days' duration. He also had just no-

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\*The capsules were supplied by Parke, Davis and Co., Detroit through the courtesy of E. C. Vonder Heide, M.D.

## BENADRYL IN TREATMENT OF ERYTHEMA—PINKUS

ticed a blister on his upper lip. He took a total of five capsules of fifty milligrams Benadryl within three days and the eruption cleared up.

Another more severe attack in January, 1946, again responded quickly to similar small doses (fifty milligrams three times daily, a total of twenty capsules).

*Case 2.*—A. M., a white girl, aged five years, was referred to me on December 21, 1945. She had had an attack of polyarthritic pain and swelling accompanied by an erythematous eruption three weeks previously. Pain and cutaneous lesions had gradually subsided under salicylates given by mouth, but the skin had flared up two days before in spite of continued medication. Examination showed a well developed girl, appearing listless, but not acutely ill, having bluish-red macular, partly confluent lesions without vesiculation on the hands, thighs, and legs. Salicylates were stopped, and Benadryl, fifty milligrams twice a day, was substituted. The eruption began to fade within twenty-four hours and had entirely cleared up by December 26, leaving only slight pigmentation.

*Case 3.*—J. V., a white girl, aged thirty-three months, had been vaccinated 14 days before coming to my office. Eight days later she had broken out with lesions which were at first considered flea bites. On examination she presented gyrated confluent erythematous plaques with purplish, partly hemorrhagic, center on the neck, over the shoulders and upper part of the chest, and on the hips. Face and extremities were clear. There was a severe crusted vaccinia lesion, almost three cm. in diameter on the left thigh. The patient was given 25 mg. of Benadryl by mouth four times daily. The lesions began to improve after twenty-four hours and faded completely within four days.

*Case 4.*—Mrs. C. L., a white woman, aged twenty-five, was being treated for tinea of the feet and eczematous dermatophytid of the hands when she developed large plaques of erythematous lesions on the flexor surfaces of both arms and forearms. She gave a history of having taken some "cold tablets." The lesions faded completely within two days, leaving only slight pigmentation after the patient took 50 mg. of Benadryl twice a day.

### COMMENT

Idiopathic erythema multiforme is usually considered a toxic manifestation of an undetermined systemic infection. This opinion is supported by the fact that erythema-multiforme-like eruptions are concomitants of various definite infections, or are caused by certain drugs. That the erythema multiforme type of cutaneous response is a hyperallergic reaction of the organism is suggested by the frequent association with articular swelling and pain which are a well known part of hyperallergic states (e.g. Arthus phenomenon). Even typical contact poisons like poison ivy may produce erythematous lesions in severe cases, with or without injudicious intramuscular administration of the extract.

The experience that Benadryl is effective in cutting short the pathologic process in erythema multiforme, and that fairly small doses have an almost immediate effect, certainly supports the hypothesis that an allergic mechanism is involved, and that the individual is in a hyperreactive state.

It has been the general experience that Benadryl has only temporary

## BENADRYL IN TREATMENT OF ERYTHEMA—PINKUS

antihistaminic effect, and that the symptoms recur quickly after the discontinuation of the drug if the causative factor is not eliminated. Erythema multiforme is a self-limited disease. This makes it plausible that Benadryl can exert here a seemingly curative influence. However, recurrences may be expected later on, as is shown in Case 1.

It could be expected that Benadryl would work similarly well in toxic erythemas of medicamentous or infectious origin, and the two cases in which I had occasion to use the drug bear out this expectation.

### SUMMARY

Benadryl was used in two cases of idiopathic erythema multiforme in which high doses of sodium salicylate had produced only temporary alleviation. The cutaneous and general symptoms were relieved in both cases with surprising promptness by comparatively small doses of Benadryl. Two later recurrences in one case also responded quickly to the same therapy. One case of toxic erythema following vaccination, and one of erythematous drug eruption subsided with similar rapidity.

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CONTACT DERMATITIS. Oscar Swineford, Jr., University of Virginia. Read at the Atlanta meeting of the Southeastern Allergy Association.

A series of slides were shown which summarized the conventional ideas of the signs, symptoms location, pathogenesis, diagnosis, treatment, and prognosis of contact dermatitis. Contact allergens were classified, history taking was outlined, the importance of location at onset was emphasized, patch tests were described and their interpretation discussed. The selection of allergens for testing was discussed. The results of routine patch testing in 160 patients were summarized as were the results of individualized patch tests in the same 160 tests.

Headquarters  
Benjamin Franklin Hotel  
Philadelphia, Pennsylvania

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Chairman and Director  
ETHAN ALLAN BROWN, M.D.  
HARRY L. ROGERS, M.D.  
J. WARRICK THOMAS, M.D.  
LEON UNGER, M.D.  
FRED W. WITTICH, M.D.

AMERICAN COLLEGE OF ALLERGISTS  
FALL GRADUATE INSTRUCTIONAL COURSE IN ALLERGY

Under the auspices of  
The Jefferson Medical College, Philadelphia

Monday, November 4 to Saturday, November 9, Inclusive

DETAILED INFORMATION—REGISTRATION BLANK—SCHEDULE OF FACULTY

The regular fall, intensive, graduate continuation course in allergy will be held at the Jefferson Medical College, Philadelphia, commencing Monday, November 4, and extending to Saturday, November 9, inclusive.

Final registration will commence at 8:00 a.m., November 4. The daily hours of instruction will extend from 9:00 a.m. to 1:00 p.m., and from 2:00 p.m. to 6:00 p.m. Various lectures will be accompanied by graphic demonstrations of all kinds—lantern slides, colored films, charts, and clinical demonstrations. Printed comprehensive abstracts of lectures, with space for notes, will be placed on sheets perforated to fit a standard ring book and will be furnished to each registrant.

All hotel reservations should be made directly through the office of the Secretary, American College of Allergists, 423 La Salle Medical Bldg., Minneapolis 2, Minnesota. Be sure to state exact time desired for reservation. Twin-bed rooms only are available.

The fee for the course is \$100. For those in military service or discharged less than six months from military service the tuition is reduced to \$25. A limited number of scholarships are available to residents and interns interested in allergy or on an allergy service. Application for such scholarships should be made to the Office of the Secretary, 423 LaSalle Medical Building, Minneapolis 2, Minnesota, and they will then be referred to the Committee for that purpose.

Members of the College, as well as candidates for Active and Associate Fellowships and non-members, are urged to register before November 4 by mail.

REGISTRATION BLANK

.....  
Date

To be completed and mailed to:  
Office of the Secretary,  
American College of Allergists,  
423 La Salle Medical Building,  
Minneapolis 2, Minnesota.

(Type or Print).....  
Last Name Initials

.....  
Street City Zone State

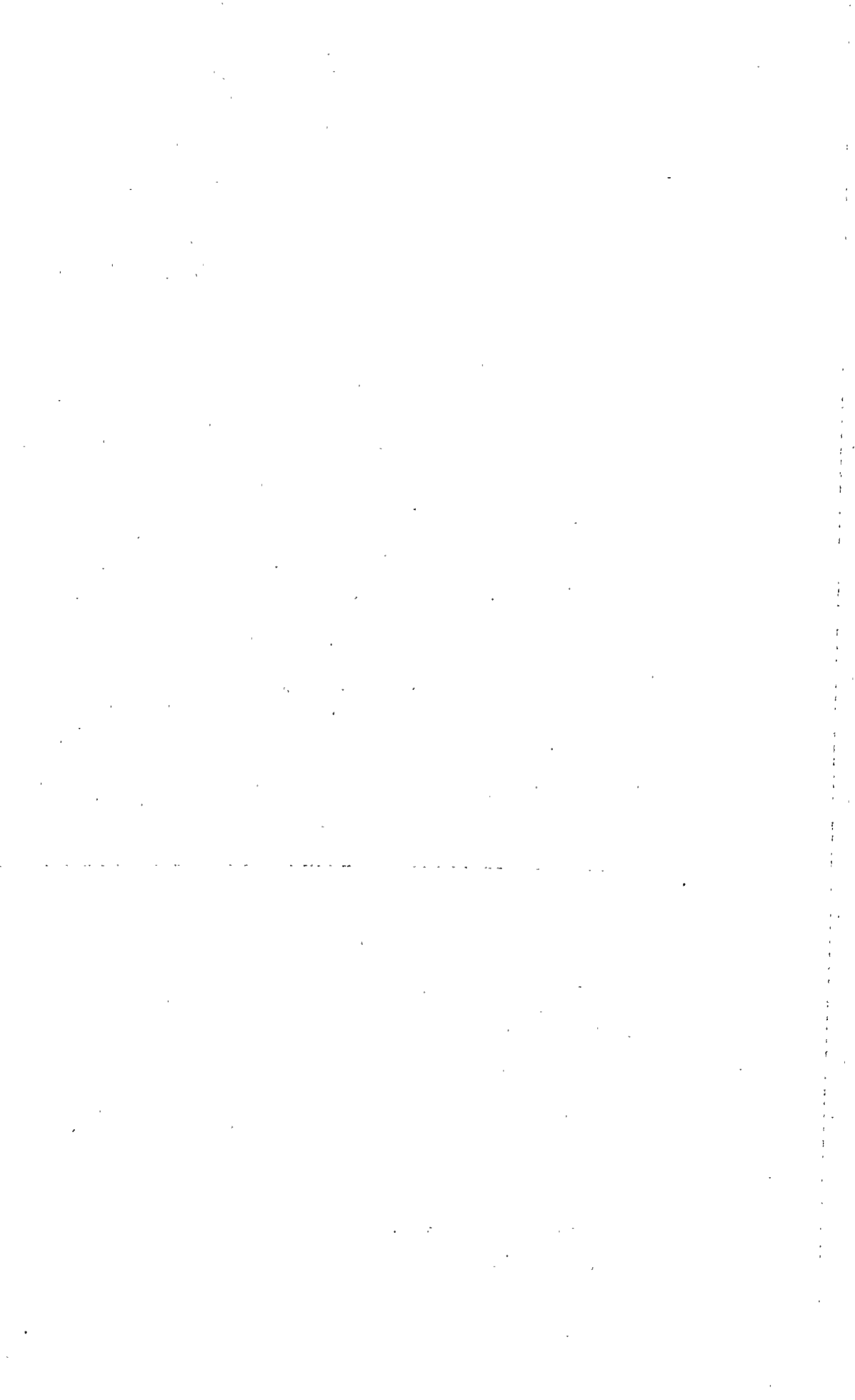
Check or Money Order Enclosed ☐

Will Remit at Time of Registration ☐

Member ☐

Non-member ☐

Candidate ☐



## SCHEDULE OF COURSES AND FACULTY

Monday, November 4

- A.M. *Fundamentals of Allergy*
- 8:00- 9:00 Registration
- 9:00- 9:10 Address of Welcome  
WILLIAM HARVEY PERKINS, M.D., Dean, Jefferson Medical College, Philadelphia, Pennsylvania
- 9:10-10:00 Role of Histamine in Allergy  
HAROLD A. ABRAMSON, M.D., Columbia University, New York, New York
- 10:00-11:30 Physiological Aspects of Allergy  
CHARLES F. CODE, M.D., Mayo Clinic, Rochester, Minnesota
- 11:30-12:30 Pathology of Allergy  
MORTON McCUTCHEEN, M.D., University of Pennsylvania School of Medicine, Philadelphia, Pennsylvania
- 12:30-12:45 Orientation  
GEORGE E. ROCKWELL, M.D., Chairman
- P.M. *Fundamentals of Allergy and Therapy*
- 2:00- 3:00 Immuno-Chemical Aspects of Allergy  
FRED W. WITTICH, M.D., Minneapolis, Minnesota
- 3:00- 4:00 Anti-Histamine acting Substances  
RALPH L. MAYER, M.D., Chief Bacteriologist, Ciba Pharmaceutical Products
- 4:00- 6:00 Clinical Use of Histamine  
BAYARD T. HORTON, M.D., Mayo Clinic, Rochester, Minnesota
- 7:30 Informal Dinner  
Speaker: LEON UNGER, M.D., President, American College of Allergists  
Subject: *Opportunities and Pitfalls in Allergy*

Tuesday, November 5

- A.M. *Therapy*
- 9:00- 9:45 Value of X-ray in Allergy; Diagnosis and Treatment  
PAUL C. SWENSON, M.D., Professor of Radiology, Jefferson Medical College, Philadelphia, Pennsylvania
- 9:45-10:30 Medical Emergencies in Allergy  
J. WARRICK THOMAS, M.D., Graham-Thomas Clinic, Richmond, Va.
- 10:30-11:00 Anti-biotics in Allergy  
HOBART REIMANN, M.D., Professor of Medicine, Jefferson Medical College, Philadelphia, Pennsylvania
- 11:00-11:30 Vaccines: Their Preparation and Use  
GEORGE E. ROCKWELL, M.D., Milford, Ohio
- 11:30- 1:00 Materia Medica and Pharmacology of Drugs Used in Allergy  
ETHAN ALLAN BROWN, M.D., Tufts Medical School, Boston, Massachusetts
- P.M. *Special Allergies*
- 2:00- 3:00 Bacterial Allergy  
M. SCHERAGO, Professor of Bacteriology, University of Kentucky, Lexington, Kentucky
- 3:00- 3:30 Mold Allergy: Pathogenic Molds  
FRED W. WITTICH, M.D., Minneapolis, Minnesota
- 3:30- 4:30 Allergy from Drug and Biological Products  
BRET RATNER, M.D., New York University College of Medicine, New York, New York
- 4:30- 5:30 Physical Allergy  
CECIL KOHN, M.D., Kansas City, Missouri

### Wednesday, November 6

- A.M. *Respiratory Allergy*  
 9:00-10:00 Allergic Rhinitis  
                   FRENCH K. HANSEL, M.D., Washington University, Saint Louis, Missouri
- 10:00-11:00 Allergic Bronchitis, Bronchiectasis, and Loeffler's Syndrome  
                   J. WARRICK THOMAS, M.D., Graham-Thomas Clinic, Richmond, Va.
- 11:00-12:30 Bronchial Asthma  
                   HARRY L. ROGERS, M.D., Jefferson Medical College, Philadelphia, Pennsylvania
- 12:30- 1:00 Bronchoscopy in the Treatment of Asthma  
                   LOUIS CLERF, M.D., Jefferson Medical College, Philadelphia, Pennsylvania
- P.M. *Respiratory Allergy (continued)*  
 2:00- 3:00 Inhalation Therapy of Asthma  
                   ALVIN L. BARACH, M.D., Columbia University College of Physicians and Surgeons, New York, New York
- 3:00- 3:45 Cardiac Asthma  
                   LEON UNGER, M.D., Northwestern University Medical School, Chicago, Illinois
- 3:45- 4:30 Status Asthmaticus,  
                   HAL DAVISON, M.D., Emory University, Atlanta, Georgia
- 4:30- 6:00 Bronchial Asthma in Infants and Children  
                   M. MURRAY PESHKIN, M.D., Columbia University College of Physicians and Surgeons, New York, New York

### Thursday, November 7

- A.M. *Dermatologic Allergy*  
 9:00-10:00 Dermatologic Allergy in Children  
                   JEROME GLASER, M.D., University of Rochester Medical School, Rochester, New York
- 10:00-11:00 Atopic Dermatitis  
                   STEPHEN EPSTEIN, M.D., Marshfield Clinic, Marshfield, Wisconsin
- 11:00-12:00 Contact Dermatitis  
                   RUDOLPH BAER, M.D., New York Post Graduate Medical School of Columbia University, New York, New York
- 12:00-12:45 Urticaria  
                   JONATHAN FORMAN, M.D., Ohio State University Medical School, Columbus, Ohio
- 12:45- 1:15 Poison Ivy  
                   LAWRENCE J. HALPIN, M.D., Cedar Rapids, Iowa

### P.M. *Concurrent Laboratory and Clinical Sessions*

<i>Laboratory Session</i>	<i>Pediatrics</i>	<i>Asthma Clinic</i>	<i>Hay Fever Clinic</i>	<i>Dermatology Clinic</i>	<i>Neuro-Allergy</i>
Skin tests Patch tests Passive transfer Nasal smears Molds Extraction methods Standardization  UNGER HANSEL WITTICH PRINCE HALPIN ROCKWELL	Special problems in asthma, hay fever, dermatitis  PESHKIN GLASER	ROGERS UNGER DAVISON BARACH CLERF	MOORE LOVELESS WODEHOUSE	EPSTEIN BAER FORMAN HALPIN	Movies  HORTON  Clinic  KENNEDY CLARKE

Friday, November 8

A.M. *Hay Fever*

- 9:00- 9:30 Botany  
ROGER WODEHOUSE, Ph.D., Associate Director of Research in Allergy, Lederle Laboratories, Pearl River, New York
- 9:30-11:00 Diagnosis and Treatment of Hay Fever  
MERLE MOORE, M.D., University of Oregon Medical School, Portland, Oregon
- 11:00-11:30 Chemical Nature of the Pollen Antigen and the Types of Extracts Used  
GEORGE E. ROCKWELL, M.D., Milford, Ohio
- 11:30-12:30 Immunology of Hay Fever: Perennial and Booster Dose Therapy  
MARY LOVELESS, M.D., Cornell University Medical College, New York, New York
- 12:30- 1:00 Low Dosage Therapy  
FRENCH K. HANSEL, M.D., Washington University, Saint Louis, Missouri

P.M. *Special Allergies*

- 2:00- 3:30 Food Allergy  
ORVAL R. WITHERS, M.D., University of Kansas School of Medicine, Kansas City, Missouri
- 3:30- 4:00 Ménière's Disease  
BAYARD T. HORTON, M.D., Mayo Clinic, Rochester, Minnesota
- 4:00- 4:45 Migraine  
FOSTER KENNEDY, M.D., Cornell University Medical College, New York, New York
- 4:45- 5:30 Ocular Allergy  
A. R. RUEDEMAN, M.D., Cleveland Clinic, Cleveland, Ohio
- 5:30- 6:15 Epilepsy  
T. WOOD CLARKE, M.D., Utica, New York

Saturday, November 9

A.M. *Special Allergies*

- 9:00- 9:45 Reactions to blood transfusions and Blood Dyscrasia due to Allergy  
HAROLD W. JONES, M.D., Philadelphia, Pennsylvania
- 9:45-10:15 Joint Allergy  
BELA SCHICK, M.D., New York, New York
- 10:15-10:45 Aural Allergy  
HUGH KUHN, M.D., Hammond, Indiana
- 10:45-11:15 Common Air Molds and Their Relation to Allergy  
HOMER PRINCE, M.D., Baylor University Medical School, Houston, Texas
- 11:15-11:45 Shock Therapy in Allergy  
GEORGE E. ROCKWELL, M.D., Milford, Ohio
- 11:45- 1:00 Office Management  
HOMER PRINCE, M.D., Baylor University Medical School, Houston, Texas
- 1:30 Luncheon  
Round Table Discussion



## SENSITIVITY TO THIAMINE HYDROCHLORIDE A Potential Hazard in a Common Office Procedure

H. T. ENGELHARDT, M.D., F.A.C.A., and V. C. BAIRD, M.D.  
Houston, Texas

RECENTLY we have had occasion to observe a patient who presented the criteria necessary for the diagnosis of sensitization to thiamine hydrochloride. A review of the available literature on this subject reveals that only fourteen<sup>1-10</sup> such cases have been reported, and in less than one-third of these have sufficient studies been carried out to clearly establish that the reaction is an allergic one. Certainly, this does not correctly reflect the incidence of this alarming and dangerous phenomenon. These cases suggest the desirability of investigating the possibility of hypersensitivity to thiamine to patients who have received parenteral injections of this material previously. We should also be alert for the development of sensitivity during the administration of a series of injections.

### CASE REPORT

A single, white woman, aged forty-two, who had no previous symptoms of allergy was first given 1 c.c. of a preparation containing thiamine hydrochloride 10 mg., nicotinamide 50 mg., riboflavin 1 mg. subcutaneously twice a week for six weeks, starting in May, 1945. After about a two-month interval she started receiving 100 mg. of thiamine hydrochloride subcutaneously twice a week. After her third injection she reported that she became nauseated and vomited and was extremely restless all night long. Twenty days later when she received her last injection she was given only 50 mg. because of previous reaction. Within one minute the patient became nauseated and vomited. She became very weak with a fast pulse; complained of substernal tightness and shortness of breath and intense itching over entire body. There were large urticarial wheals over arms and face. She had marked conjunctivitis. She was given 5 min. of epinephrine and after a few minutes the itching and wheals disappeared. She was able to leave the office in thirty minutes and the next morning felt fine and had no after-effects.

The presence of Prausnitz-Kustner antibodies was established by a definite reaction to 0.02 cubic centimeters of thiamine hydrochloride in a non-allergic individual.

### COMMENT

The sequence of events in this case indicates that the reaction was a truly allergic phenomenon. The patient tolerated well a substance which was originally harmless, but which later caused a mild and then a severe systemic reaction. The presence of antibodies was demonstrated by means of passive transfer to a non-sensitized individual.

All of the reported cases reacted in a similar fashion except Mitroni's.<sup>7</sup> This patient presented the reaction after the first injection, and this physician concluded that the organism was sensitized biologically with natural thiamine and responded allergically to the crystallized form.

Detailed discussion of these cases should serve little useful purpose because of their great similarity. One report, that of Schiff<sup>7</sup>, serves to illustrate well how serious the reaction can be. His patient, a white woman, aged forty-five, who previously had a course of thiamine chloride by needle, reacted in the following fashion to one injection:

"On December 28, about one or two minutes after receiving her injection of thiamine hydrochloride into the buttocks (from a 5 c.c. vial from which she had had six previous injections), the patient became nauseated and vomited. A thin, colorless fluid issued from her nose; she voided involuntarily and collapsed. Her skin was covered with a cold perspiration. She was pulseless and had ceased breathing and her heart sounds were inaudible. She was placed on a table in shock position and surrounded with covers. Artificial respiration was started and 1 c.c. of epinephrine hydrochloride was injected intravenously and  $7\frac{1}{2}$  grains (0.5 Gm.) of caffeine with sodium benzoate intramuscularly. Her blood pressure could not be obtained at first. About half an hour later her pulse was palpable and her blood pressure was 110 systolic and 70 diastolic."

The review of these cases emphasizes certain important points. We feel that reactions to thiamine hydrochloride are of much greater frequency than published reports would lead one to believe. These data emphasize the importance of using specific therapy properly, and whenever practical, to give it orally. Only in very rare instances is it necessary to administer thiamine hydrochloride intravenously. In individuals who are allergic to this substance, one may either hyposensitize them or give the medication orally.

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1216 Main Street

## MALARIA AND URTICARIA

MAJOR HAROLD H. GOLZ, MC, F.A.C.A.

A case of generalized urticaria as a prominent and prodromal manifestation of malaria has recently come under the observation of the author. Review of the literature available in this theatre fails to reveal the previous report of any similar case. Stitt and Strong<sup>2</sup> in their text on tropical medicine merely mention in a sentence that urticaria may be seen in malaria. Horn and Karelitz<sup>1</sup> in their review of 1,155 cases of malaria do not mention urticaria as a symptom although they devote a paragraph to the discussion of cutaneous manifestations. It is therefore felt that this case is of sufficiently unusual interest to warrant its being brought to the attention of the medical officers in this theatre.

### CASE REPORT

A. J. T., Pfc., aged twenty-four. Service: two years. Nativity: Pennsylvania.

This soldier was admitted to the Orthopedic Service of this station hospital on 27 March 1944 because of an internal derangement of the right knee which had been incurred in 1940. The family history revealed that his father had died of pneumonia at the age of fifty, and his mother had died of unknown cause in a mental institution at age of fifty-six. Three siblings had died of influenza during the 1918 epidemic. Two siblings are living and well. There was no family history of allergic diathesis. The soldier's previous health had always been excellent. He had never had a serious illness nor was there any past personal history of allergic disorder. He had had a tonsillectomy in 1940. Prior to entry into the armed forces he had been a college student.

The patient was first seen by the author at 1300 hours, 15 April 1944 in consultation with the Orthopedic Service. At this time he exhibited a severe attack of generalized urticaria and angioneurotic edema of the entire face. This attack had started thirty minutes previously. The patient supplied the history that he had had a similar but milder attack at 1800 hours on 13 April 1944. This attack had been reported to the ward nurse but no treatment had been deemed necessary. On 14 April 1944 lesions were rapidly disappearing and no new ones had made their appearance since the previous evening. The patient further stated that the only time previously that he had had hives was in August 1943 at the onset of his first and only attack of benign tertian malaria. The lesions at that time were not severe and persisted for only twenty-six hours. Further examination of the patient's history and hospital record revealed that at no time had he ever had symptoms to suggest allergic rhinitis, asthma, food or drug idiosyncrasy, serum sickness, migraine or eczema. Furthermore he had had no immunizations or parenteral therapy of any kind within the previous two months and at no time during his current hospitalization had he had any type of medication, oral or parenteral. Therapy for his knee had consisted of an adhesive strapping applied several weeks before and heat with a light cradle started ten days previously. To neither treatment had he had any untoward reaction. Examination of the hospital menus for the previous several days revealed no foods that he had not previously eaten with impunity on frequent occasions.

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## MALARIA AND URTICARIA—GOLZ

On physical examination the patient showed an extensive severe urticaria involving the entire skin surface with small and giant wheals. There was no portion of the skin as large as one square inch that was not involved. The skin of the face, eyelids and lips was markedly swollen but there was no laryngeal involvement. The spleen and liver were not felt and the remainder of the physical examination was normal. Complete blood count and urinalysis were normal.

During the following twenty-four hours the patient required five injections of epinephrin hydrochloride 1:1000 in 0.3 c.c. doses and ephedrin sulphate grams 0.048 every four hours orally to control his symptoms. He was immediately placed on a diet consisting of only boiled rice, canned pears, sugar and water and this diet was continued until 18 April 1944. By noon of 16 April 1944 all symptoms and lesions had disappeared and the patient felt as well as usual. At 1000 hours 17 April 1944 the patient experienced the onset of another severe attack of urticaria and angioneurotic edema exactly similar to that of 15 April 1944 and again he required repeated injections of epinephrin for relief. By the morning of 18 April 1944 all lesions had again disappeared. Up to this time the patient had never had an elevation of his temperature above normal and no elevation of his pulse rate above normal except after injections of epinephrin. On 18 April 1944 intradermal tests were made with the following pollens and inhalants: Ragweed, careless weed, house dust, duck, chicken and goose feathers, horse, cat, dog and rabbit dander, sheep wool, cottonseed, orris root and kapok. These tests were negative in all dilutions. Because of the tertian periodicity of these three attacks of urticaria and the history of a similar attack at the onset of an attack of malaria in 1943 it was first suspected that these lesions might represent a manifestation of a subclinical recurrence of his malaria in spite of the absence of rigors and other common symptoms. A blood film was then carefully examined and found to be positive for plasmodium vivax with a very low degree of parasitization. Atabrine 0.2 grams was given immediately and repeated at six-hour intervals for five doses. At 1000 hours, 19 April 1944 the patient experienced a sharp shaking chill immediately followed by the appearance of three to four urticarial wheals on both hands and feet, and his oral temperature was recorded at 101.6 degrees Fahrenheit. During the ensuing twelve hours his temperature dropped to normal and so remained for the duration of his hospitalization. Atabrine was continued for five days in doses of 0.1 gram, three times daily. At no time after 19 April 1944 did the patient have any recurrence of his hives nor was there any further rise in his temperature. He had felt quite well and had been eating the regular house diet since 18 April 1944. The patient was discharged to duty on 3 May 1944, blood smears for malaria after completion of treatment being negative.

### COMMENT

It seems fair to conclude that here we were dealing with urticaria and angioneurotic edema as a prominent manifestation of recurrent tertian malaria. The patient had had three attacks of urticaria unaccompanied by chill or fever at approximately forty-eight-hour intervals before he experienced a typical mild malarial rigor with fever and his history reveals one similar episode in 1943 during the course of his initial attack of malaria. In the interpretation of these phenomena it appears that each of the first three attacks occurred in association with the maturation of succeeding cycles of parasites in which the degree of parasitization was not sufficiently great to provoke the usual signs and symptoms of a malarial paroxysm. With the fourth attack accompanied by chill and fever the serum concentration of atabrine was probably sufficiently high to modify the allergen-reagin mechanism, and only a mild allergic seizure took place. In order to explain the mechanism of

*(Continued on Page 298)*

# GENERALIZED CHRONIC DERMATITIS DUE TO TATTOO

## Report of Case

BOEN SWINNY, M.D., F.A.C.A.  
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FOUR of the five previously reported cases of dermatitis due to tattoo have been localized in or about the areas of tattoo. The case presented herewith is unusual in that the dermatitis was chronic and widespread, and occurred many years following the tattooing. It is evident in this case that the tattoo was the cause of the dermatitis because: (1) the red areas of the tattoo were highly irritable; (2) contact tests with mercurials were positive, and (3) the patient has remained well for six years following the surgical excision of the tattoo.

Unna's<sup>5</sup> case had itching, swelling and small vesicles in the red area of his tattoo but none in the India ink part, the reaction occurring after the application of mercury to his hemorrhoids. The sixty-three-year-old patient had been tattooed in his youth and had had mercury by inunction at the age of forty-three. Patch test with mercurial plaster gave a positive reaction.

Ballin<sup>1</sup> reported a twenty-year-old man, tattooed two years previously, who for two months had had itching, swelling and oozing in the red but not in the blue areas of his tattoo, with normal skin otherwise except a slight tendency toward seborrhea. Positive patch tests with 2 per cent ammoniated mercury ointment and 1:1000 solution corrosive sublimate and negative tests with patch and scratch of cinnabar were obtained.

Madden's<sup>2</sup> patient, aged twenty-seven, had immediate raised inflamed and painful reaction in his tattoo; this reaction subsided except in the red areas which remained elevated, scaly and slightly pruritic. No tests were reported.

Novy<sup>3</sup> reported the case of a man with a generalized macular brightly erythematous eruption with most severe involvement of chest and abdomen and eyes almost closed with edema, thirty-six hours after tattooing. Vesiculation and bleb formation were present everywhere the red dye had been used and the hands (the dorsal aspects of which were the sites of tattoo) and forearms were badly swollen. The skin lesions and edema disappeared. All the dyes that had been used in the tattoos were used in contact tests and the only positive was with the rose which contained cinnabar. Pure cinnabar produced a stronger reaction. A positive reaction to U.S.P. ammoniated mercury ointment and a suggestive positive to 1:1000 aqueous merthiolate were obtained.

Sulzberger, Kanof and Baer<sup>4</sup> reported the case of a man, aged twenty-two, who had been tattooed four months previously with blue and red. The red areas had been swollen and itchy for two or three weeks and an external medicament had been applied. Following this, the swollen areas

## DERMATITIS DUE TO TATTOO—SWINNY

had become scaly and crusted. Patch tests with calomel powder and with mercuric bichloride 1:1000 were reported as "1 to 2 plus" and with 10 per cent sulphur precipitate, 3 per cent cinnabar and 2 per cent mercuriochrome negative.

### CASE REPORT

R. L. Y., an electrician, aged thirty-one, presented himself in October, 1939, with an exfoliative, pruritic, weeping dermatitis of six months' duration. The lesions were widespread with greatest severity in the cubital and popliteal fossae where the disease began. The major lesions spread confluent over the upper arms and shoulders and there were discrete follicular and smaller confluent areas over the trunk and extremities. For about three years before the eczematous type of lesion began, there had been several recurrent attacks of urticaria of the evanescent type. The family and past history were negative for allergic diseases. Extensive study for foods by intradermal testing and elimination diets was done with entirely negative results. There was no blood eosinophilia. Occupational and home contacts were studied. After six months of unsuccessful treatment, the patient brought to my attention the irritability of the red areas in his tattoo, which he had had for fifteen years. Stroking or gently massaging these areas caused immediate pruritic whealing flares which passed away in twenty or thirty minutes. There were no eczematous areas in or adjacent to the tattoo. Contact tests were positive within twenty-four hours to 2 per cent ammoniated mercury ointment and 1:1000 bichloride of mercury. Both caused reddening and swelling at the sites of application.

The entire tattoo (covering an area 2.5 by 3 inches on the inner aspect of the right forearm) was excised surgically and replaced by skin graft by Dr. Asa Beach of San Antonio in July, 1940. Within two months the skin was entirely well except for thickening of the cubital and popliteal areas.

The patient returned to my care in March, 1946, for the treatment of an eczema of recent occurrence about the ear wherein a sulfathiazol ointment had been used for otitis externa. He had had no recurrence of eczema or urticaria during the six years until the present episode. The thickening of the skin had entirely disappeared. Contact with mercury at this time was negative.

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# Editorial

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*The opinions expressed by the writers of editorials in the ANNALS are individual and do not necessarily represent the group opinion of the Board or of the College.*

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## THE SAN FRANCISCO CONVENTION

When one considers the distance the majority of the members had to travel under trying transportation difficulties, and with very limited hotel reservations, the Second Annual Meeting of the American College of Allergists was comparatively largely attended. Outstanding allergists and immunologists representing practically every specialty in medicine enthusiastically participated and entered into interesting discussions. Headquarters were at the Clift Hotel, and the three-day Scientific Session was held in the Roof Lounge, June 28 to 30.

Robert Doerr, M.D., Ph.D., Professor Emeritus of Hygiene and Bacteriology at the University of Basel, Switzerland, was guest speaker. Doctor Doerr was unanimously elected an Honorary Fellow of the College. His paper on the "Integration and Differentiation of Allergic Phenomena" will appear in the September-October issue of the ANNALS OF ALLERGY. Prior to the convention, Doctor Doerr was a guest of the College at an informal dinner in New York City and in Boston, to which his former close friends and associates in the East were invited.

The fact that many of the papers were outstanding was shown by the excellent news reports of the Associated Press, the San Francisco newspapers, *Science News*, and the C.B.S. Broadcast from New York City on the evening of July 2.

The first Pan-American Congress on Allergy was held in the afternoon session of the first day of the program. Owing to marked travel restrictions several South American delegates could not attend. The opening address of Dr. Guido Ruiz-Moreno, President of the Argentine Allergy Society, was read by the Chairman in his absence.

The next Pan-American Congress will be held at some future time either in one of the South American countries or Cuba. The College appreciates the honor of having held the first Congress under its auspices.

At the regular session there were so many outstanding papers that it would be unfair to feature any particular one. The anti-histaminic drugs received due attention and discussion. Although most of the papers were based upon original scientific investigations, their practical clinical application to the diagnosis and treatment of allergic diseases was stressed.

The Symposium on Mold Allergy was largely attended, and new problems of extraction and standardization were presented and discussed.

The Board of Regents wish to take this opportunity to thank the members and friends of the College who so ably participated in the program and discussions.

## EDITORIAL

### FALL GRADUATE INSTRUCTIONAL COURSE IN ALLERGY

In this issue is a colored tear-out sheet, including registration blank, announcing the schedule of courses and faculty of the College's Annual Fall Graduate Instructional Course in Allergy. Please read this information carefully.

No effort is being spared by the thirty-eight instructors, the majority holding high teaching positions in outstanding medical schools in the country, to satisfy the registrants, whether they are advanced students of allergy wishing to refresh their knowledge of the subject, those training for specialization in allergy, or non-specialists seeking graduate training.

The Educational Committee urges that as many members of the College as possible, as well as candidates for Active and Associate Fellowships and non-members, avail themselves of this opportunity and register early. All registrants will receive printed outlines of the courses as well as the Manual of Allergy Laboratory and Diagnostic Procedures.

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### MALARIA AND URTICARIA

*(Continued from Page 294)*

these events one must assume that the parasite is the allergenic excitant, that the skin is the only shock organ, that the parasite is not capable of exciting the shock organ when it is confined to the red blood cells or the viscera, and that it acts as an excitant only when free in the plasma.

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**BENADRYL, ITS THERAPEUTIC VALUE IN ALLERGY.** Bowen, Ralph: *Texas State Medical Journal*, July, 1946.

This is mainly a report on one of the anti-histamine drugs, Benadryl. The description, physical properties, pharmacology, toxicological studies, dosage, et cetera, are presented in detail. The author gives a special warning in the administration of Benadryl to patients who have been taking sedatives, such as the opium derivatives and the barbiturates. Based on his own clinical experience and that of others, he also warns that Benadryl should not be given to a patient sensitive to aspirin, since both contain a coal tar radical, and cites severe reactions to Benadryl in patients sensitive to aspirin.

As with the majority of other observers, he noticed that it is most effective in the urticarial group. A case of horse serum sensitivity in a two-year-old baby is cited; after all the usual therapeutic measures to combat this case of serum sensitivity, which was extremely severe and alarming, as high as 100 mg. of Benadryl was given by mouth, followed by 50 mg. every four hours for dosage; then 50 mg. every six hours for twenty-four hours. There was a complete recovery, and the author cites that, in an emergency, children can be given more Benadryl as originally proposed; also, that Benadryl is a great aid in serum cases. Allergies of all types were treated by the author with Benadryl. He concluded that the drug has a true place in allergy, and it is most effective in cases of chronic urticaria. He also noted improvement between 60 and 70 per cent in ragweed sensitive patients. He found that it was of great aid in relieving itching in the eczemas of children.

He concludes by warning that Benadryl should not be used to the exclusion of proper allergic investigation and management, and that Benadryl should be considered only as an adjunct in the management of the allergic cases.

# Progress in Allergy

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## BRONCHIAL ASTHMA Annual Critical Review of Recent Literature

LEON UNGER, M.D., F.A.C.A.  
Chicago, Illinois

New books and articles dealing with asthma have appeared since my review of the 1944 and 1943 literature.<sup>193,194</sup> Some earlier foreign articles have recently become available and are included in this review.

Some important papers have been published but many are of a general nature. This is not said in criticism as all of these reviews are educational to those who write them or hear them or read them in medical journals. In many cases such papers whet the author's appetite to do clinical or other types of research.

### NEW BOOKS

Coca, Crieip, Moretti and Bula, Taub, Unger, and Wodehouse, in alphabetical order, have written new books. Coca's Second Edition of "Familial Non-Reaginic Food Allergy"<sup>33</sup> states that the most common cause of variation of pulse rate, which is a constant, physiological to each individual, is familial non-reaginic food allergy or idioblapsis. Right or wrong, few allergists have accepted his theories; very few have even tried his method of diagnosis and treatment. This is unfortunate, especially when one realizes how much allergy owes to Doctor Coca.

Crieip's "Essentials of Allergy"<sup>37</sup> is a very compact manual in which the author does a good job in covering the whole field, clinical as well as immunological. It is particularly well fitted for the student and practitioner. Details and theories are largely omitted because of the demand for a small book. The section on asthma is good.

Moretti and Bula<sup>126</sup>, from Montevideo, have a paper-covered book on "Allergia." It is based on their 217 allergic cases, of which 121 were respiratory, with 105 cases of asthma. The book discusses the importance of allergy in all specialties, and deals chiefly with respiratory, digestive, dermatologic, and neurologic allergic conditions. Pollens cause only 5 per cent of allergic diseases in their section of Uruguay. Food allergy is most important, followed by that due to inhalants, molds and bacteria.

Taub's<sup>186</sup> small manual on "Essentials of Clinical Allergy," for students and practitioners, contains a good deal of information.

Unger's monograph on "Bronchial Asthma"<sup>195</sup> is "by far the most pretentious book on the subject of bronchial asthma that has been published in recent years."<sup>25</sup> The author attempted to cover the various aspects of this condition as thoroughly as possible, with special regard to bibliography and the clinical side of asthma. He hopes he has succeeded in suggesting to students, practitioners and allergists the steps by which diagnosis and treatment can usually be adequately handled. A section of the book deals with the military side of allergy and with allergic diseases other than bronchial asthma, but the emphasis is on asthma itself.

The subject of "Hay Fever Plants" is well discussed in Wodehouse's book.<sup>207</sup> It is so authoritative that no one interested in allergy can afford to be without it. The subject of pollen and pollen surveys is especially interesting.

## PROGRESS IN ALLERGY

Other recent books on subjects related to allergy contain useful information. These are "Manual of Clinical Mycology" by Conant and others<sup>36</sup>; Landsteiner's "The Specificity of Serological Reactions"<sup>103</sup>; Gilman's "Manual of Soil Fungi"<sup>64</sup>; Mansmann's "Manual of Allergy Lectures for Nurses"<sup>113</sup>; and Sevag's "Immuno-Catalysis."<sup>168</sup>

Edgren's book<sup>18</sup> deals chiefly with "eczema," though its association with asthma is also discussed.

### TROPICAL EOSINOPHILIA, LOEFFLER'S SYNDROME, PERIARTERITIS NODOSA

Confusion exists in differentiating these three conditions. All are usually characterized by high blood eosinophilia. Are they identical?

The reader is urged to reread the summary on tropical eosinophilia and Loeffler's syndrome which appeared in the March-April, 1945, ANNALS OF ALLERGY.<sup>193</sup> The earlier papers were discussed. *Tropical eosinophilia* occurs chiefly, but not exclusively, in the tropics, especially in India. The chief symptoms are an insidious onset, with malaise, low-grade fever, headache, and unproductive cough; wheezing and dyspnea are often associated. Leukocytosis (up to 60,000) and marked blood eosinophilia (up to 89 per cent) are striking features. Chest x-ray films usually show fine mottling in both lungs. One to six intravenous injections of neoarsphenamine or other arsenical products causes prompt relief with disappearance of leukocytosis eosinophilia, and the so-called "asthma." No causative organisms have been found.

Apley and Grant<sup>9</sup> report five more cases of tropical eosinophilia among 114 consecutive soldiers who were returned to England from the East because of various chest diseases. Only these five had pronounced blood eosinophilia despite the fact that ninety-six cases of bronchitis, asthma, or both, were in this group. The distinction between this disease and Loeffler's syndrome is not sharp; they may be manifestations of the same disease. They therefore urge therapeutic trial with an arsenical even if the diagnosis of tropical eosinophilia is tentative; the possibility of dramatic results warrants such an effort. A patient of Hirst and McCann<sup>89</sup> had never been in India, but his symptoms of two years' duration were typical of this condition. He had 15,520 leukocytes, with 72 per cent and 82 per cent eosinophiles. Films merely revealed increased bronchial markings. Skin and routine laboratory tests were negative for parasites. Neoarsphenamine was given, and a dramatic clinical cure occurred within three weeks. They also urge therapeutic trial with arsenicals.

Hodes and Wood<sup>91</sup> report two soldiers just returned from the Orient in whom relief also followed neoarsphenamine. The eosinophilia reached 92 per cent. The authors do not believe that the etiologic role of the cheese mite, *Tyroglyphus*, and related parasites has been established, even though these have been reported in the sputum of patients with "eosinophilic" lungs. Some of the patients develop chronic bronchopulmonary symptoms. Soysa and Jayawardena<sup>173</sup>, from a military hospital in Southeast Asia in the past two years, have observed many asthmatic patients. A number of these had high blood eosinophilia (40-80 per cent) but rarely gave a previous or family history of asthma. In a study of thirty Ceylonese soldiers with this condition, they believe that inhalation of mite-laden air was responsible. *Tyroglyphus* and *Tarsonemus* mites were found in the sputum of some of these patients. The majority had been exposed to dust from rice and other cereals, pulses, flour, sugar, tea, coffee, cheese, dried fish, dehydrated vegetables, spices and other condiments, and various other dry rations and grocery products such as are issued in bulk. Some had been exposed to stores of military equipment and miscellaneous articles, and these mites are known to exist in such places. The symptoms dragged on until oral administration of carbarsone and

## PROGRESS IN ALLERGY

acetasone often brought quick relief. Some of these soldiers also were infested with such worms as *Ancylostoma duodenale*, but the usual anthelmintic treatment produced no reduction in the percentage of eosinophiles.

*Loeffler's syndrome* has not been neglected. Blanton<sup>21</sup> describes four patients who gave either a personal or family allergic history. An injection of 0.50 c.c. of epinephrin in three of these cases removed shadows previously seen in the lungs, but these shadows returned later. He believes the condition is due to an allergic localized edema, simulating angioneurotic edema. Miller's<sup>121</sup> patient had a migrating pulmonary infiltration which lasted three months. The high blood eosinophilia (64-85 per cent) disappeared after treatment with mapharsen. The sputum also contained many eosinophiles.

Spector<sup>174</sup> emphasizes the contrast between the paucity of physical signs and the extensive but temporary and migratory consolidations of varying size, as shown by x-ray. If endamebae are found, relief of symptoms and disappearance of parasites usually follow two daily 1.0 c.c. injections of emetine hydrochloride. Randall's patient,<sup>150</sup> with typical clinical and radiologic findings of Loeffler's syndrome, was dramatically cleared by ten daily intramuscular injections of emetine. This raises the question, especially in districts in which amebae are endemic, as to the relation of amebae to the syndrome.

From Palästine is a description by Lyon and Kleinhaus<sup>112</sup> of three patients with eosinophilia and transitory pulmonary infiltrations. Cutaneous manifestations were associated; there were transient swellings of the skin and mucosa over wide areas of the body; the skin was red or edematous in places and even resembled furuncles. Itching, pain, and tension were present, and swellings migrated for two to eight days or longer. No parasites were found, and in a few cases biopsies were also negative for parasites. Eosinophilia was found in the sternal marrow and in the affected tissues. Several patients with marked cutaneous infiltrations had normal lung x-rays. Wright and Gold<sup>208</sup>, on the other hand, report twenty-six cases of creeping eruption (Cutaneous helminthiasis); nine of these patients developed transient migratory pulmonary infiltrations with a paucity of symptoms and physical signs, but with eosinophilia in the blood and sputa. Skin tests with either *Ascaris* or *Trichina* extracts were positive in twenty-three of the twenty-six cases. There was no correlation between the degree of skin sensitivity and the clinical findings.

And now comes evidence that Loeffler's syndrome may be identical with or closely related to periarteritis nodosa. Bayley and his associates<sup>13</sup> examined the lungs of a woman, aged fifty-nine, who died of Loeffler's syndrome. The bronchial lesions were similar to those observed in bronchial asthma, i.e., the predominantly eosinophilic exudate infiltrating all portions of the wall, the hyalinization and thickening of the basement membrane of the epithelium, and the large quantities of mucus in the cells and lumina. The advanced organization of the pneumonic exudate and the granulomatous character of the focal lesions prove that the pulmonary lesions are *not* transitory in all cases. Arteries and arterioles showed marked necrosis, histologically quite similar to changes found in periarteritis nodosa. Hennel and Sussman<sup>86</sup> also report two deaths in five cases of Loeffler's syndrome, proved clinically and by x-ray. Biopsy in one revealed the necrotizing lesions of periarteritis nodosa. These authors state that the pulmonary lesions, as shown in films, tend to be homogeneous and of variable size. Narrow plate-like densities frequently extend obliquely caudad and laterally, a type of shadow apparently unique to this disease. Lesions may simulate those found in tuberculous bronchopneumonia or phases in the course of Boeck's sarcoid. Pierce and associates<sup>141</sup> believe Loeffler's syndrome has an allergic background, and suggest that transient focal pulmonary edema occurs rather than consolidation. They also state that the condition often resembles periarteritis nodosa.

## PROGRESS IN ALLERGY

Broch's patient<sup>27</sup>, a woman, aged twenty-eight, died five minutes after the initial use of a 10 per cent epinephrin spray (in this country we advise the 1 per cent solution). The patient had asthma for a year, and was in the hospital with a diagnosis of "transient pulmonary infiltration;" the blood eosinophilia was 70 per cent. It was estimated that not more than 0.10 to 0.15 mg. of epinephrin had been inhaled, and the author does not regard the drug as the cause of death. At autopsy, thickening of the interstitial tissues between alveoli and infiltration with lymph and plasma cells were found. Some lung tissue was completely obliterated and spaces were filled with lymph, plasma and eosinophilic cells. A "great and widespread distribution of eosinophiles" was marked.

An interesting article comes from Germany. Schlect<sup>162</sup> reproduced eosinophilic lung infiltrations experimentally. Guinea pigs were sensitized by intratracheal sprays of serum and were killed after six, twenty-four, and forty-eight hours. Macroscopically, the lesions resembled those of pneumonia, with involvement of a whole lobe. Eosinophiles were found in the secretions after six hours but not after twenty-four hours. Microscopically, the alveoli were partly filled with a material which largely consisted of eosinophiles. Eosinophiles were also present in the entire bronchial and peribronchial structures and in the blood. Thus there is a parallel between the microscopic findings in Loeffler's syndrome in the human and these experimental allergic infiltrations. Therefore, Loeffler's syndrome must itself be allergic and eosinophilia an essential finding in allergy.

*Periarteritis nodosa* has been further discussed. Rich<sup>152</sup> reports death in a patient who was given iodine for hyperthyroidism. Autopsy revealed characteristic arterial and arteriolar necrosis in visceral organs. Rich<sup>153</sup> also reports fatalities after treatment with antipneumococcus serum and after sulfonamides, singly or combined; autopsies were diagnostic of periarteritis nodosa. Rich believes these therapeutic agents sensitize the patients, and he warns against the use of sulfonamides for minor ailments. A soldier was circumcised; fever occurred; four grams of sulfadiazine were given daily for nine days; death occurred forty days after admission, and Rosenak and Maschmeyer<sup>156</sup> believe that the histologic findings of periarteritis nodosa were probably due to sensitivity to the drug.

Wilson and Alexander<sup>205</sup>, in 300 consecutive cases of periarteritis nodosa, found bronchial asthma in fifty-four, or 18 per cent. All but three of forty-seven of these cases (94 per cent) showed high eosinophilia (11 to 84 per cent, with average 53.5 per cent). This is in marked contrast to 151 cases without asthma in which there were only nine instances of hypereosinophilia (6 per cent), with an average eosinophile percentage of 2.5. Washburn and Otto<sup>202</sup> report autopsy findings of periarteritis nodosa in a twenty-one-year-old soldier who had hay fever and died after removal of the gall bladder.

### MILITARY REPORTS

Articles still appear from various camps and hospitals. Medical officers agree that allergic individuals, especially those who have asthma, are frequently of little value in the various branches of the service. Some of these doctors have, however, by energy and perseverance, succeeded in helping many of these persons, and have thus been able to keep many in the service who would otherwise have had to be discharged.

Zanfagna<sup>2,11</sup> analyzed 100 cases of perennial bronchial asthma in the Fourth Service Command. The family history of asthma was positive in sixty-five of these cases, with another 9 per cent positive for other allergies. Psychic factors often produced attacks in predisposed patients. Marked positive skin tests to one or more common inhalants were found in ninety-two cases. Allergy clinics were established in each army post throughout the command, and the soldier was

## PROGRESS IN ALLERGY

kept in service, if possible. The usual therapeutics, including hospitalization, was carried out, and no serious complications occurred.

From the Oliver General Hospital, Augusta, Georgia, Rudolph<sup>160</sup> summarized 200 cases of bronchial asthma, with an enormous morbidity. Statistics: 67.5 per cent positive family history; 90 per cent aged twenty to thirty-five years; 79 per cent had less than thirty months of service prior to final disposition; in 85 per cent asthma started prior to induction; in 15 per cent the onset was incident to service; in 54 per cent overseas service was associated with onset or aggravations of symptoms; 92 per cent had associated allergic conditions or complications or some coexisting disease. The Certificate of Disability Discharge had to be given to 61 per cent; 23.5 per cent were given limited duty; 11.5 per cent were returned to full duty; and 4 per cent were transferred to Veterans' Hospitals.

Leopold<sup>165</sup> also analyzed 200 soldiers, white and negro, who had chronic perennial bronchial asthma and had returned from overseas. One hundred eighty-three (91.5 per cent) were from tropical regions, seventeen (8.5 per cent) from North Africa, England, Aleutians, Iceland, or Southern Italy. His statistics: sixty-three patients (31.5 per cent) had their first attack while overseas; 138 (69 per cent) were nineteen to twenty-eight years old, inclusive; fifty-four (27 per cent) were twenty-nine to thirty-eight, and eight (4 per cent) were thirty-nine or older. Of the new cases, 88.9 per cent developed asthma while in areas with a hot, humid climate; 137 (68.5 per cent) had asthma prior to induction, but in some the asthma had ceased in civilian life; in many, asthma had been present for more than ten years with continuing symptoms in army camps in the United States. Asthma in this group was not severe, but a marked increase in frequency and severity of attacks occurred while overseas. Asthma continued after return to this country in 95.5 per cent. Climatic factors were believed important in 159 cases (79.5 per cent); high humidity and frequent rains were especially aggravating.

From Fort Eustis, Virginia, Blank and Levitt<sup>20</sup>, from June 1, 1941, to December 31, 1943, discuss the military aspects of allergic rhinitis; asthma was associated with the nasal condition in 104 of the 741 cases (13.8 per cent). The authors personally observed the importance of grass pollen in North Africa, Italy and Sardinia; the main season was from late April through June, though some cases occurred as late as the end of August or the beginning of September. They point out the possible danger from sneezing while in advanced posts.

From the San Antonio Aviation Cadet Center a booklet has been published on "Allergy in the Army Air Force."<sup>184</sup> Hampton discusses the Allergy Laboratory which was established in 1942 to insure uniformity throughout the air forces. All major AAF hospitals were to have qualified allergists, if possible. From May, 1943, to May, 1945, 70,814 c.c. of extracts were prepared, and 67,316 c.c. of 10,000 protein-nitrogen units per c.c. were supplied to sixty other AAF hospitals. This allergy laboratory became well staffed with medical corps and air corps officers, including allergists, a botanist, mycologist, bacteriologist, biochemist, medical technicians, and laboratory assistants. The functions of the laboratory: preparation of extracts, standardization on PN content, Seitz filtration and sterility tests, shipping extracts to other AAF installations, pollen counts, collection of pollen, survey of airborne fungi, and culture of airborne fungi from which to make extracts.

Despite rejections at induction centers, Hampton notes 4,942 patients in this part of the hospital from August 1, 1942, to May 1, 1945; of these, 3,705 were allergic and 1,237 were proved non-allergic after diagnostic surveys. Interesting findings: the percentage of allergy in officers was much higher than in the enlisted men; 75 per cent of all hospitalized patients had bronchial asthma; all skin tests were intracutaneous; bacterial examinations of the sputa were routine

## PROGRESS IN ALLERGY

in asthmatic patients, and autogenous vaccines were made if significant bacteria were found, but in most cases stock respiratory vaccines were used. Neuro-psychiatric consultations were frequent. Treatment of some asthmatics was aided by sulfonamide therapy, but penicillin was not of much value. In fifty cases of intrinsic asthma, intravenous injections of typhoid vaccine (10-250 million) were given, usually three times; the results were variable but some patients were benefited. Hampton has tables concerning the classification, the diagnosis, and the incidence of the allergic patients.

Steen's contribution to this bulletin deals with the treatment of hay fever and seasonal asthma. He discusses the four seasons in San Antonio due to trees, grasses, and weeds, as well as to the mountain cedar which is so rampant in this region in December, January, and February. Injections are given pre-seasonally, co-seasonally and perennially.

Bieberdorf and Hampton add a nice article on "Hay Fever Exciting Plants in the Southwest;" the most important are mountain cedar, oak, hackberry, pecan and mesquite trees, Bermuda and Johnson grass, tall and false ragweeds and amaranthus. Russian thistle and sagebrush are frequent in the more western areas.

Hampton and Bieberdorf also discuss "Airborne Fungi in Allergic Disease." The survey at this San Antonio hospital lasted from November 1, 1943, to November 1, 1944. They exposed their plates for two minutes daily, facing the wind; they also exposed thirty slides daily for twenty-four hours. *Hormodendrum* appeared throughout the year and in October comprised 59 per cent of the total monthly count, but alternaria were most consistently found, especially in December and February. *Helminthosporium* was highest in June, August, September and October but was sporadic. *Spondocladium*, *fusarium*, *pullulari pullulens*, *phoma*, *aspergillus* and *penicillia* were also found. The slide method counts did not always coincide with those made by the plate culture method. Johnson grass smut was the chief smut found, with a high count of 540 on July 23, 1944. Some rusts appeared.

In 186 of 1,515 allergic patients (12.28 per cent) marked positive reactions were found on intracutaneous testing to one or more mold extracts of 1,000 PNU per c.c. or less. Only six of 488 normal controls gave marked reactions. Respiratory allergy was present in 180 of this group, and thirty of these gave negative tests to all common pollen and inhallant extracts. The authors stress the importance of mold extracts in diagnosis and treatment.

Hinnant deals with the general principles of management and disposition of allergic diseases. He states, "A clearly defined allergic state with a favorable prognosis is the only justification for continued allergic therapy (i.e. in military service)." Elimination of foods, dusts, et cetera are difficult in the service. Experience shows that allergic rated flying personnel with other than mild pollinosis are better off grounded and assigned within the Continental United States. Richiardi and Hampton then discuss the preparation and the standardization of extracts by the PNU method.

Kaufman and Ditkowsky<sup>89</sup> describe a Navy hospital with over 200 asthmatic patients. It is located near a desert region in Banning, California, selected because the environment is helpful to many allergic patients—high altitude, equitable climate, and low pollen and mold counts. Asthma existed prior to enlistment in 65 per cent, and was not previously present in 15 per cent; the other 20 per cent were allergic but had no previous asthma before entrance into the service. Most of the patients had been overseas, chiefly in New Guinea, Philippine, Solomon and Admiralty Islands; this foreign service led to aggravation of symptoms in about 90 per cent of cases. After arrival in this hospital, symptoms of hay fever were lessened in about 90 per cent of cases; 40 to 50 per cent of the asthmatic patients improved.

## PROGRESS IN ALLERGY

Moreno<sup>124</sup>, from Buenos Aires, states that the Argentine law requires every male citizen nineteen to twenty-one years old to register for military service. He advises military surgeons to examine and skin test all those who claim to be or are actually allergic. If the survey shows that the candidate cannot be a good soldier he should be assigned for one year to non-military service.

### ETIOLOGY OF ASTHMA

The importance of mold allergy is becoming more and more recognized. Allergists in the Eastern United States have been reluctant, for the most part, to ascribe any but a minor role to fungi as a cause of asthma and allergic rhinitis; this is undoubtedly due to the fact that mold, smut and rust counts are lower in that section than in the midwest, the deep south, and the Pacific Northwest. The recent war has emphasized the importance of fungi in damp hot climates.

The work of Hampton and his associates in the AAF has already been discussed.<sup>184</sup> Hampton and Lowe<sup>76</sup> prepared their mold extracts with the use of a ball mill. In 358 allergic patients, fifty-seven (15.9 per cent) gave positive intracutaneous tests to 1:100 alternari or mixed mold extracts, and fifty-four of these individuals had respiratory allergic conditions, including sixteen with bronchial asthma. All ninety-two control persons, on the other hand, gave negative intracutaneous tests with these extracts. Reactions to molds alone occurred in sixteen of the fifty-seven patients; thirty-two were also positive to pollens, twenty-one to other inhalants, and four to foods. The authors used the skin tests to pollens, molds, and other antigens as a method to determine if their cadets were fit for flying. Nasal eosinophilia was found in forty-seven of fifty-four patients with respiratory mold allergy.

Blumstein and McReynolds<sup>23</sup> surveyed the mold situation in the Philadelphia area. They, too, found it necessary to use both the plate and slide methods because of wide variations in counts with each. Each has advantages and disadvantages, but both showed elevations during warm and damp days of spring and summer. Their major mold season was mid-May to mid-October. The larger spores, especially alternaria, were more prominent during this time, and also hormodendrum and smuts. They found no direct correlation between meteorologic conditions and mold counts, but hourly spore counts varied, and spore showers were frequently observed. Blumstein<sup>24</sup> found that 41 per cent of 406 allergic patients gave positive intracutaneous skin tests to one or more of thirteen mold extracts. Of these, twelve patients were clinically sensitive to molds only, i.e., 3 per cent of the entire group or 9 per cent of those with seasonal symptoms only. These twelve patients had seasonal symptoms corresponding to the periods of greatest mold concentration. Asthma was present in ten of these twelve, while eight were also allergic to pollens. He used a provocative nasal test to confirm clinical sensitivity. Alternaria, hormodendrum, monilia, helminthosporium, cephaloroseum, and mucor were most important. In patients with seasonal symptoms and negative pollen tests, molds rather than pollens may therefore be responsible. He also points out, as is well known, that itching of the eyes rarely occurs in mold-sensitive patients, in contrast to its frequency in those allergic to pollen; and also stresses the long mold season (May to November) as compared with the relatively short pollen seasons. He found specific positive passive transfer reactions in ten of these twelve mold-sensitive individuals.

One must disagree with his statement that "mold extracts should not be used routinely for skin testing because of the low incidence of sensitivity in the allergy group as a whole." If he routinely tests all of his respiratory allergic patients with mold extracts the incidence of positive reactions will reward his efforts.

Harsh and Allen<sup>82</sup> studied airborne fungi for three years in San Diego,  
JULY-AUGUST, 1946

## PROGRESS IN ALLERGY

California, and the vicinity, a section with peculiar weather conditions. Both plate and slide methods were used. The authors report 131 distinct species, comprising twenty-seven known genera. The most important: *hormodendrum*, *alternaria*, yeasts, *penicillium*, *macrosporium*, *sporotrichum*, and *helminthosporium*. Those of lesser importance included *botrytis*, *epicoccum*, *pleospora*, *chaetomium*, *aspergillus*, *stemphyllium*, and *pringshema*. Certain genera occur with increasing frequency from the beach inland; with others the reverse is true. More children than adults were mold-sensitive; this was not true in pollen allergy. The authors also determined the amount of protein in the more important extracts as well as the comparative rate of solution of each; also the approximate size and shape of the main fungi.

Two short papers come from the Hawaiian Sugar Planters Association. Larsen<sup>104</sup> points out that these islands have a relatively small land area completely surrounded by ocean, hence their pollen problem can never be as bad as in most mainland communities. In 100 patients he found positive skin tests: dust, thirty; Bermuda grass, twenty-eight; *algeroba*, twenty; amaranths, thirty; sugar cane, ten; Johnson grass, twelve. A "false ragweed" does occur in Hawaii as well as short ragweed, but the incidence is small. H109 sugar cane is a heavy pollen producer, but is being rapidly replaced by a number 32-8560, which does not produce pollen. *Algeroba* trees, important pollen producers, are being blown down and other trees which do not cause hay fever are being substituted. There are fifty-nine varieties of grass, and Larsen urges destruction of amaranths.

Weller<sup>203</sup>, also from Hawaii, states that most pollen is discharged when the relative humidity is high (85 to 95 per cent); the pollen discharges as early as 2 to 3 a.m.; and the amount increases as dawn approaches at 6 to 7 a.m. The amount of discharged pollen decreases if the humidity is too low (60 to 70 per cent), or too high (90 to 95 per cent). Gentle breezes increase the pollen counts. Perennial hay fever occurs with two or three peaks. The main causes are: (A) Grasses, especially Bermuda, known in the Islands as *Maniania*; red top; sugar cane (*Saccharum officinarum*) which flowers from November to January, and whose pollen is 30 microns in diameter as compared to the 20 micron Bermuda grass pollen. (B) Amaranths are widely distributed and give off abundant pollen. (C) *Algeroba* occur more in outlying districts and suburbs than in the cities, and the pollen is important, though bee-borne. Other possible pollens are those of ironwood, false ragweed, and *Haole Koa* (*Leucaena glauca*), a widely distributed member of the Composite group. Fungus spores are numerous, especially *helminthosporium*, and an unidentified round black spore case filled with small hyaline spores.

From Palestine come three reports by Gutmann.<sup>73</sup> One deals with a peculiar form of rhinitis, probably non-allergic, which occurs during "khamseen" days when the wind blows from the east (desert); another discusses 180 cases of vernal conjunctivitis and concludes that allergy to molds plus a chronic bacterial infection are responsible. The third paper, "Allergy in Palestine" is statistical. About 3 per cent of the Jewish population of Palestine has one or more major allergies, as contrasted to the approximate 10 per cent in America and somewhat lower percentage in Europe. Although exact statistics among Arabs have not been obtained, allergic diseases are known to be more common than among the Jews. (In a certain quarter of the town of Nablus, Doctor MacLenen found the extraordinarily high percentage of 80 per cent of asthma in Arabs applying for medical examinations). Gutmann never found such high percentages. Asthma occurred in approximately 0.90 per cent of the Jews in Palestine, but in Jerusalem the percentage was about twice as high. Gutmann states that the incidence of asthma is increased by climatic conditions; i.e., "the main causative factor of the disease is the mold fungi (mildew) which flourishes as the result of the dampness of the

soil or the atmosphere, factors which are of much greater importance in the humid atmosphere of the coastal regions than in the mountainous districts." The incidence of allergic diseases in Palestinian children is more than twice as high as in European children. Asthma constituted 36 per cent of all allergic cases; 17 per cent were classified as allergic rhinitis, and 3 per cent as hay fever, for a total of 56 per cent respiratory allergy. The other 44 per cent of allergic conditions included patients with urticaria, gastrointestinal diseases, migraine, et cetera.

There are some recent reports on miscellaneous causes of asthma. From Australia, Sutherland<sup>182</sup> isolated a polysaccharide-containing-fraction from house dust by adsorption of an aqueous extract on benzoic acid. The adsorbed material was dried and dissolved in water, centrifuged, and the clear supernatant fluid precipitated with acetone. The purified material proved more active than the original adsorbate, gave no reactions for proteins, and lost much of its activity when Seitz-filtered. Scratch and intracutaneous tests with the adsorbed fraction showed great activity without irritation. For treatment the author recommends a 1:10,000 dilution at first but could usually reach 1.0 c.c. of the 1:100 dilution. In 100 patients allergic to house dust, Sutherland found no constant association between sensitivity to house dust and any other allergens which might be in house dust; he therefore believes house dust contains a unique allergen. All patients who gave positive scratch tests with the usual dust extracts gave larger reactions to the more refined fraction. This work is important and calls for further studies by the author and others.

Osgood's patient<sup>134</sup> had severe paroxysmal cough, with rhinitis and dyspnea. In 1942 caroid powder was dusted into the site of vein ligations. In 1944 her husband began to use tooth powder which contained caroid. Three days later the patient's rhinitis and conjunctivitis began, followed shortly by attacks of asthma. Eosinophilia was present in the blood and sputum. Hospitalization on three occasions brought prompt relief but symptoms recurred when the patient went home. The caroid tooth powder was observed and removed and symptoms ceased. Intracutaneous tests with 0.02 c.c. of a 1:500 and 1:50 caroid extract were strongly positive and were followed by a terrific constitutional reaction (flushing face and hands, confusion, pallor, perspiration, vomiting, labored breathing, imperceptible pulse, fall of blood pressure to 60, and coma). Heroic treatment with tourniquet, epinephrin, et cetera, brought recovery in two hours, though weakness remained, and was followed by severe urticaria for five days and swelling of skin test sites from the shoulder to the forearm for three days; the skin was still not entirely normal after four months. Passive transfer tests to caroid extract were positive in dilutions of 1:500, 1:5,000, 1:50,000, and 1:500,000; precipitins were not demonstrated, and no deviation of complement was shown. Caroid extract was tested intracutaneously in forty other patients: moderate reactions occurred in four, slight in seven, none in twenty-nine; there were no untoward results. The medicinal uses of caroid (papain) are discussed.

Wiseman and McCarthy-Brough<sup>206</sup> had an even worse experience. Their seventy-eight-year-old female patient died within fifteen minutes after seventeen intracutaneous tests; the usual therapy with epinephrin subcutaneously, intravenously and even intracardially failed. The patient had had asthma since the age of four years, had been successfully treated with vaccine and dust extract at seventy-two, and resumed treatment at seventy-eight when asthma returned. The extracts used in testing were chiefly inhalants; most of them contained 1,000 protein nitrogen units per c.c.; reactions were numerous and fairly large before the constitutional reaction occurred. The authors conclude that in the aged, despite skin atrophy, reactivity to skin tests may be acute; the aged require the same meticulous care in testing and in treatment as in any other age group.

## PROGRESS IN ALLERGY

These last two reports are instructive. One patient died after intracutaneous tests and the other almost died. Those of us who do preliminary scratch tests never have the worries which must be inherent in those who begin their skin test routine by the intradermal method. We make our scratch tests in utter safety. If we obtain all the necessary information as indicated by the patient's history, intracutaneous tests are usually not necessary. But if the scratch tests are negative, we fearlessly run through the intracutaneous set of tests because patients who give negative scratch tests practically never develop constitutional reactions. In other words, the caroid powder, for example, could have been rubbed into a scratch on the arm and a large positive reaction would have almost certainly developed, with safety for the patient; then, if intracutaneous testing was thought advisable, dilutions of 1:1 million to 1:1 billion might have been tried.

Bernton's patient<sup>15</sup>, a man of thirty-six years, had rhinitis and later asthma and conjunctivitis when exposed to burlap sacks. These bags must have been in contact with castor bean because (a) skin tests were positive only with castor bean pomace and with burlap slivers from a sack; (b) large positive passive transfer tests were obtained with dilute doses of the non-toxic allergenic fraction isolated from castor bean (CB-1A); and (c) the uterine horn of a pig previously sensitized to this fraction contracted when an extract of the burlap bag was added to the Dale bath—therefore, the bag contained this castor bean fraction. An intradermal test of a 1:1 million dilution of this fraction was positive on this patient. Castor oil seems to be free of CB-1A. Castor bean protein is very potent, and hyposensitization is usually not warranted; but I am now attempting to carry this out, beginning with a 1:1 billion dilution, in an asthmatic man who handles fertilizer containing castor bean, who gives huge positive scratch reactions to castor bean, and who is unable to change occupations. Intradermal tests were positive in dilutions of 1:1 million to 1:1 billion; weaker dilutions were not tried. Asthma from castor-seed meal is also discussed by Steiner.<sup>177</sup>

Zanfagna<sup>210</sup> reports edema, urticaria, and asthma from ingestion of sulfathiazole. The asthma persisted ten days. Feinberg and Watrous<sup>55</sup> found asthma and rhinitis in fourteen workers who were exposed by inhalation to small amounts of dust of chloramine-T and halazone. These chemicals were manufactured and packaged at this plant. Relief followed removal from the vicinity, but symptoms occurred in some workers as far away as 300 yards when contaminated air reached them through the exhaust. The authors state that these simple chemicals of low molecular weight behave like true atopens because they found immediate skin whealing, and also obtained positive passive transfer (this latter finding demands further study as passive transfer to date with drugs and chemicals has been extremely rare). The authors theorize that: (a) such simple chemicals may act as complete antigens; (b) simple chemical allergens, not yet identified, may be present in food, drink and air; (c) chemical irritants, hitherto regarded as acting in a non-specific manner, may, on re-examination, exhibit specific allergenic behavior.

Silica may be allergenic, according to Habeeb.<sup>74</sup> Male patients in a tuberculosis sanatorium in San Antonio were studied for two years; there were 134 coal miners and 582 who were not miners. Eosinophilia in the blood was found in 51.2 per cent of miners with silicosis and in 32.4 per cent of miners with silicötuberculosis. On the other hand, only 16.1 per cent of miners with tuberculosis and only 5.9 per cent of non-miners with tuberculosis had eosinophilia. The greater the percentage of eosinophiles, the greater is the amount of silicosis and resultant emphysema.

In England, Hunter, Milton, and Perry<sup>92</sup> blame platinum. Rhinorrhea, sneezing, dyspnea, wheezing, and cough occurred in fifty-two of 91 workers exposed to the dust or spray of complex salts of platinum; thirteen of these also had a scaly

erythematous dermatitis. No symptoms occurred in workers exposed to high concentrations of metallic platinum or to complex salts of other metals; e.g., palladium. Radiologic and blood studies in these patients were essentially negative. Lesser<sup>107</sup> discusses allergy to aspirin and suggests Duke's tongue test.

Pipes<sup>142</sup> studied 370 consecutive allergic patients, of whom 229 had respiratory symptoms, with no reference as to whether or not they smoked. In thirty-five, respiratory symptoms were precipitated or aggravated by proximity to tobacco smoke. In forty-seven (13 per cent), intracutaneous tests were positive for tobacco smoke extract, with negative reactions in ten non-allergic controls. There was a correlation of positive history and positive skin tests in nineteen cases. By exhaustion passive transfer tests Pipes showed that tobacco extract and tobacco-smoke extract contain different antigens; one cannot exhaust the other. Allergy to tobacco smoke is probably an entity distinct from that due to tobacco itself. Both extracts should be used in routine testing.

From France comes the unique idea of Blamoutier<sup>18</sup> that in allergy of gastrointestinal origin the patient may be sensitive to the decomposition products of protein digestion rather than to the food itself. In allergic patients certain foods cause urticaria even though skin tests to those foods may be negative. In sensitization by the respiratory route, however, skin tests are usually positive to the exciting food. His patient had skin trouble for ten years, due to lamb or mutton. Skin tests with the meats and with samples incubated in gastric or duodenal juice were negative. But skin tests with specimens which had been incubated in *both* gastric and duodenal secretions gave positive skin and passive transfer reactions. This report may be important; further study is advised.

Typhus, yellow fever, influenza, and Rocky Mountain spotted fever vaccines are cultivated in chick embryo tissue or yolk-sac. Egg-sensitive individuals have had severe reactions from these vaccines. Sprague and Barnard<sup>175</sup> report two cases in ensigns: one developed severe asthma, angioneurotic edema and urticaria after the first immunizing dose of yellow fever vaccine. Past history revealed hay fever, eczema and asthma, with extreme sensitivity to eggs and nuts, and with strong positive skin tests to egg white, ragweed, horse serum, et cetera. The other officer received a mixture of typhus and typhoid vaccine and tetanus toxoid; two hours later, generalized edema, dyspnea, coryza and dysphagia occurred. The past history showed eczema, hay fever, and high grade egg-sensitivity. The authors urge inquiry regarding sensitivity to egg before injecting typhus or yellow fever vaccine; if the history is positive they advise skin tests for egg; the vaccine is to be injected only if the skin test is negative. Roth<sup>158</sup> found that four of nine patients who had constitutional reactions after typhus vaccine gave a history of egg allergy; he also urges precautions. Raynolds<sup>151</sup> discusses two Army nurses who gave a definite history of egg-sensitivity on being questioned prior to inoculation with typhus vaccine. Both were tested intradermally with 1:100 and 1:10 dilutions of typhus vaccine. One gave an immediate large skin reaction; in fifteen minutes the other nurse developed an intense itchy blotching of the face, neck and back, and epinephrin was necessary. Neither nurse was given the usual typhus fever inoculation.

Stull<sup>181</sup> also urges caution in this regard. He reports thirteen anaphylactic reactions following the use of an egg-containing vaccine, with one death after a combined inoculation for cholera and typhus. Park's thirty-five year old British airman<sup>138</sup>, with a life-long history of acute sensitivity to egg, almost died within thirty minutes after his first injection of antityphus vaccine (prepared from yolk sac). Inoculation later with yellow fever vaccine (prepared from chick embryo) did not produce reactions. Skin tests were strongly positive for both egg extract and undiluted typhus vaccine. Rubin<sup>159</sup> recently reported angioneurotic edema, dyspnea and chest pain in a soldier within ninety minutes after injections of typhus and

## PROGRESS IN ALLERGY

yellow fever vaccines. Interestingly, skin tests were strongly positive to egg yolk but not to egg white, and the patient could eat egg white without trouble. Rubin mentions experimental work which demonstrates that although egg yolk and egg white contain antigens common to both, they also have individual antigens.

Respiratory problems in cotton and cottonseed oil mills in Mississippi were investigated by Ritter and Nussbaum.<sup>154</sup> Twelve patients were forced to leave the cotton industry because of asthma which occurred either in the cotton linter rooms or in the large seed storage bins. Asthma was precipitated in two of these patients by a trial visit to the linter room. Examinations and x-ray films showed that none of the twelve patients had any pulmonary complications, e.g., bronchiectasis, emphysema, or fibrosis. None were allergic to either the oil expressed from cottonseed or to the dust environment where the residue is ground into meal. Despite these twelve cases, the incidence of respiratory disease among workers in the cotton industry is very low.

Factors which may precipitate or aggravate asthma continue to be discussed. Anglade<sup>5</sup> studied eighty asthmatic children who were in the Lafayette Preventorium in Haute-Loire, France, at a height of 800 meters. Meteorological factors have not, in his experience, modified the intensity of attacks, nor their intervals, nor their clinical aspects, nor their frequency.

Folgueras and Toulet, from Argentina<sup>56</sup>, discuss six cases of "premenstrual" bronchial asthma. Treatment with testosterone gave good results in four; co-existing infections (sinusitis and appendicitis) were present in the two patients who failed to respond. In no case was a premenstrual increase in folliculin found, as claimed by some French investigators. Epstein<sup>52</sup> observed that dysfunction of the thyroid gland occurred in six allergic patients; four of these had asthma. The presence of the thyroid condition may not be demonstrable when the allergic disease is evident; only in later years may the thyroid factor become predominant, but one must treat the thyroid disease as well as the allergic.

Koch<sup>101</sup> discusses endocrine imbalance as a basis for allergy, and especially stresses the necessity for removal of toxic factors, relief of psychic strain, and stimulation of endocrine function, mainly of the thyroid and adrenal glands; such treatment, he states, will alleviate symptoms of acute allergy. Zondek and Bromberg<sup>214</sup> have a long article on "Endocrine Allergy." They review allergy especially as related to menstruation and menopause. They conclude that certain gynecologic disorders, e.g., pruritus vulvae, are conditioned by allergy to endogenous hormones. Such allergy also is important when menstruation or menopause plays a part in asthma, allergic rhinitis, angioneurotic edema, and urticaria. They demonstrated skin reactions to the steroid hormones: estrone, estradiol, progesterone, pregnandiol, testosterone, androsterone, or desoxycorticosterone acetate.

The psychic aspects of asthma and other allergic conditions have received attention. Karnosh<sup>97</sup> admits that allergy is important but he believes that no allergic patient can be adequately evaluated without considering the personality structure in which the disease is implanted. When allergy attacks the brain as has been claimed by allergists in discussing migraine, Ménière's disease, infantile convulsions, transient paralyses and certain cases of psychosis, Karnosh believes emotional mental and neural phenomena also occur.

Campbell<sup>29</sup>, on the other hand, derides psychoanalysis in allergy and says "the procedure finally terminates when they (psychoanalyst and patient) tire of each other or when the patient's funds are exhausted. The psychiatrist has no specially pertinent information to impart to the allergist. Every allergist knows, just as every other physician knows, that the physician-patient relationship, as per the Hippocratic Oath, implies that the doctor may make an appraisal of the intimate personal information obtained." Campbell, however, urges a careful psychic and

moral history as well as the usual and allergic, because psychic and moral influences may aggravate asthma or other allergic diseases; while such influences persist complete relief cannot be obtained. He concludes that "there are no convincing reports in the literature of any allergic patients having received any more relief from psychiatric treatment than should have otherwise occurred from wise counseling with the allergist."

Goitein and Brown<sup>67</sup> discuss asthma and solitude. In a jail population of about 600, six had asthma. These seemed to enjoy their incarceration. All had asthma of the intrinsic type, and all were dependent on drug therapy. They reacted favorably but only temporarily to each new physician and each new drug. Psychotherapy helped and when not used their drug-addictive tendencies increased. These six patients actually preferred to be in jail because drug therapy was always close at hand to alleviate asthmatic symptoms. As a group they were sullen, suspicious, querulous, resentful, cynical, and embittered. All six had been convicted of assaultive crimes.

Moreno and Bontolila<sup>125</sup>, from Argentina, report another case of spontaneous animal allergy; the authors support Wittich's contention that the word "atopy" may be applied in spontaneous animal allergy as well as in the human. In a dog with dermatitis slight positive intracutaneous skin reactions were obtained to maize, oat, cocoa and dust. Two hours later a constitutional reaction occurred, with exaggeration of the dermatitis and with tachycardia, tachypnea, dyspnea, and oliguria for twenty-four hours; relief by 1.5 mg. epinephrin. This dog was much improved when placed on a meat diet, and positive passive transfer tests were obtained on another dog; the precipitin test was negative.

## PATHOLOGY OF ASTHMA

A number of papers may be described. Unger<sup>196</sup> reported postmortem findings in five cases of uncomplicated asthma. Emphysema was present in all five, even in a one-year-old child who had asthma for nine months. Plugging of bronchi occurred in the first four cases (the lungs in case 5 were not sectioned), and this obstruction is a very important cause of asthma. Morphine was used in two cases and death followed shortly. Morphine is too dangerous a drug to use in bronchial asthma because it lessens or prevents expectoration of mucus and mucous plugs; it also depresses the cerebral respiratory center, with resultant slowing of respiration in a patient already short of oxygen. Microscopically, the usual findings were present: the thickening and hyalinization of the basement membrane of the bronchi, eosinophilic infiltration of the plugs, the bronchi and the peribronchial tissues, and excessive mucus in the lumina, varying from thin serous material to thick black obstructing plugs. The muscular layer is often thickened in chronic asthma. Emphysema is characteristic, as shown by thinning and rupture of alveolar lining and actual enlargement of alveoli. Vessel walls may be thickened. The heart was of normal size in four of these cases; there was an acute dilatation of the right heart in the first case, an uncommon finding.

Harkavy<sup>80</sup> believes that allergic conditions are due to edema of the endothelial cells of blood vessels. In asthma this edema leads to wheezing, dyspnea and cough. In eighty-seven of 132 cases of bronchial asthma, there were antecedent nasal symptoms which usually diminished as asthma increased. He divides chronic asthma into two groups:

I. Bronchial asthma with bronchopulmonary reactions with or without secondary cardiovascular complications. Infection of sinuses and lungs are frequently associated; pneumonia may occur and be followed by fibrosis and compensatory emphysema. Then the patient either has (1) repeated pulmonary infections with more and more fibrosis, emphysema and gradual pulmonary insufficiency, which

causes hypertension of the lesser circulation with frequent sclerosis of pulmonary vessels, which then leads to right ventricular strain, cardiac decompensation, and cor pulmonale—death may ultimately result from right heart failure—or (2) status asthmaticus which may develop suddenly, with resultant exhaustion and anoxemia unless tenacious sputum is removed.

11. In a much smaller group of asthmatic patients, vascular tissue reactions are much more severe. There may be migrating infiltrations in the lungs (Loeffler's syndrome). In such cases (see Loeffler's syndrome), autopsies reveal allergic inflammatory exudate with acute arteritis, with or without destruction, arteritis obliterans, and periarteritis nodosa. Electrocardiographic changes suggest damage to coronary arteries. Pleural effusion may occur, with up to 90 per cent eosinophiles in the fluid. These changes, states Harkavy, are reversible at first, but each attack of asthma may be followed by progressive vascular changes in other organs, e.g., other serous membranes, the kidneys, liver or gastro-intestinal tract. Death may follow in three to five years due to failure of a vital organ.

Milton Cohen<sup>34</sup> also discusses reversibility and irreversibility in bronchial asthma and other allergic conditions. Infectious complications cause histologic changes dependent on the particular germ, e.g., tubercle bacilli. In the non-infectious group the histologic picture is usually about the same for all antigens. In both groups the reactions may be reversible, causing no tissue damage, or irreversible, with tissue destruction and fibrosis. The two types may occur together in the same patient. Those patients whose attacks occur at long intervals, e.g., asthma due to ragweed, usually suffer no tissue damage. In intrinsic asthma, however, almost constant asthma may be associated with changes in areas which have not entirely recovered from previous reactions. The chronic inflammation thus engendered then leads to irreversible changes, tissue death, and scarring, and may progress to a fatal issue.

Saphir<sup>161</sup> states that myocarditis occurs more frequently with bronchiectasis than with uncomplicated pneumonia. In eight of 152 cases with both bronchiectasis and myocarditis the most significant clinical observation is the discrepancy between relatively slight fever and the high pulse rate. At autopsy two of these patients had hearts of normal size, six had hypertrophy of the right ventricle. Myocarditis was found histologically in all; it was recent in five cases; it may cause sudden death.

Mazzei<sup>118</sup> discusses the etiology, diagnosis and complications of intrabronchial hyperpressure during expiration. This occurs frequently in bronchial tumors, bronchial or bronchopulmonary carcinoma, and peribronchial adenopathies of carcinoma, occasionally in other pulmonary diseases. If not relieved, permanent emphysematous blebs, pseudocysts, and giant emphysema may result.

Rall, Gilbert and Trump<sup>149</sup>, by experiments done on decerebrated dogs, stimulated the nasal mucosa by blowing cold air directly into dogs' nostrils; cold water, ethyl chloride and chloroform vapor were also used. Reflex bronchoconstriction occurred, probably by way of afferent branches of the trigeminal nerve and efferent impulses down the vagus nerve. Large doses of atropin (up to 10.0 mg.) were then injected or the vagi were cut and then the nasal stimulation was repeated. Then ergotamine tartrate (0.5 to 1.0 mg.) was given and the nasal stimulation repeated. Atropine and vagotomy do not abolish this nasal reflex; ergotamine blocks the sympathetic motor nerves and does prevent the reflex.

Blanco and his associates<sup>19</sup> discuss chronaxia (minimal electrical stimulus necessary to produce a contraction in muscle tissue) of muscles in thirty-six asthmatic patients. Temporary difficulty affected inspiratory muscles in eighteen of these patients but only during and immediately after an attack. Díaz and Lorente<sup>43</sup> found no significant difference between the amount of acetylcholine in the urine of asthmatic patients during and between attacks. This chemical is found in asth-

matic sputum, but is also present in sputum from patients who have pulmonary tuberculosis or lung abscess. They found no histamine in sputum from asthmatic patients. Palacio<sup>136</sup> reviews theories regarding etiology and pathology of asthma; and Pedrera<sup>140</sup> reports death (no autopsy) in an asthmatic boy who entered the hospital in status asthmaticus and died in three and a half hours; morphine was not given.

Thomson<sup>188</sup> had a forty-seven-year-old female asthmatic who had attacks for many years and who died shortly after an injection of morphine. Autopsy revealed pulmonary findings typical of those usually found in bronchial asthma. An interesting sidelight: an ovarian teratoma was also found and this contained respiratory tissue which showed the same eosinophilic infiltration, Charcot-Leyden crystals and thickened basement membrane which were found in the lungs.

## SYMPTOMATOLOGY OF ASTHMA

Classification of asthma is discussed in four papers and in Unger's book on Bronchial Asthma.<sup>195</sup> Unger divides his cases into "paroxysmal" and "chronic," a division which can be made after the history and first examination, before skin tests. This separation of cases is very valuable because of the difference in treatment and in prognosis. The prognosis in the paroxysmal cases is usually good to excellent; that in the chronic patients fair to poor.

Swineford<sup>183</sup> classifies asthma as (1) atopic, (2) infectious, (3) mixed atopic and infectious, and (4) non-allergic, non-infectious. In this last group he includes cases due to physical allergy, bronchiostenosis, psychosomatic influences, acute failure of the left ventricle (cardiac asthma), emphysema with wheezing, so-called "intrinsic asthma," and that due to the nasobronchial reflex from nasal foreign bodies or polyps. One may question the need for his fourth group as the members really belong in one or other of the other three groups. "Cardiac asthma" is not asthma at all; it is a manifestation of disease of the cardiovascular-renal system.

Berresford<sup>16</sup> believes that asthma should be classified as regards the severity of symptoms just as patients with heart disease, malignancy and burns are classified into four degrees.

1. First degree asthma—mild. Essentially no interference with normal activity, readily controlled.
2. Second degree—moderately severe—interference with normal activities but able to work at reduced level. Simple treatment effective but required in large doses.
3. Third degree—severe asthma. Pronounced interference with normal activities. Controlled only by injections.
4. Fourth degree—very severe. Status asthmaticus. Semi-invalid or invalid. Not adequately controlled by any symptomatic therapy.

To above, one must add a secondary classification, e.g., seasonal or perennial, continuous or intermittent.

Such classification, if adopted universally, would simplify conversation and literature; for example, "third degree asthma, perennial, intermittent, two weeks" describes a patient with severe asthma who requires frequent injections to control symptoms with much loss of time to patient with attacks occurring for about two weeks throughout the year.

Berresford's classification has much to recommend it. It is simple and very descriptive, and similar classifications have been invaluable in other branches of medicine and surgery.

Graña, from Uruguay<sup>71</sup>, divides allergic disease into three groups: .

## PROGRESS IN ALLERGY

1. Histaminic type, including those due to physical agents, serum disease, hydatid cysts, and atopic (asthma, angioneurotic edema, hay fever, atopic dermatitis, urticaria).

2. Idiosyncrasy, including chemicals, drugs, oils, and essences (vegetable) or extracts.

3. Tuberculous or inflammatory, including tuberculous, fungous, hydatid liquid, and the Frei antigen.

Ludiner and Oscherov<sup>111</sup> discuss three types of asthma: allergic, bacterial and menstrual.

This reviewer prefers the classifications of Berresford and Unger as being simple and informative.

Several interesting articles have appeared on asthma and other allergic diseases in children. Glaser<sup>66</sup> has an excellent and comprehensive review of all phases of this subject. Campbell<sup>28</sup> discusses allergy in the newborn: 25 per cent of his 200 allergic children manifested allergic symptoms soon after birth. He enumerates many signs of allergy at this period, and emphasizes the frequency of asthma in nursing infants when the mothers have dandruff. This may be related to Simon's observation that human dander may be allergenic especially as a cause of atopic dermatitis in the nursing infant.<sup>170</sup>

Clein<sup>22</sup> studied 100 allergic children from birth to the age of ten years (private practice). The first allergic symptoms usually occurred in the first four months of life as a rash, eczema, vomiting or pylorospasm, with colic, excess gas, diarrhea or constipation. Egg yolk and orange juice were most often implicated at this age. Prophylactic dietary and environmental treatment were instituted at once in these infants, but 98 per cent developed major allergic symptoms during this ten-year study. Allergic rhinitis was most frequent, followed by hay fever, asthma, eczema, gastro-intestinal allergy, urticaria, or other allergic conditions. Asthma occurred in twenty-six cases, beginning from one month of age to twelve years. It was the only major allergic disease in 6 per cent of the entire series although very few cases were severe and hospitalization was rarely necessary. A few children developed a pre-asthmatic cough, without real wheezing. Rhinitis occurred in 50 per cent of the asthmatic children, hay fever in one-third, and eczema in one-third. Most cases of asthma occurred before the age of six years. Therefore, says Clein, prophylactic treatment does not prevent the onset of allergic conditions but it does minimize the severity and it does allow children to grow and develop normally, both physically and mentally. This and similar studies are very important in the coming campaigns to educate the public and the medical profession in the prevention of asthma and other allergic conditions.

Three papers come from Latin America. Dighiero<sup>44</sup> discusses 170 allergic infants; ninety had asthma, thirty asthmatic bronchitis, seventeen eczema, and eleven urticaria. A few had other allergic conditions. The interesting finding is the low percentage of pollen allergy common to almost all reports from Latin America. In this series only 2 per cent were pollen-sensitive; 35 per cent reacted to foods; 15 per cent to inhalants other than pollens; 20 per cent to both foods and inhalants. In 28 per cent, skin tests were negative. Pollen allergy is therefore of little importance in this region. Torroella<sup>189</sup> reviewed 289 allergic children. Asthma occurred in 42 per cent of these, and 48 per cent had allergy of the skin. A positive family history was present in 76 per cent, with transmission mainly through the female. Symptoms began at an average of 4.4 years of age and were more frequent in

males. Foods again were most important, but pollens, dust, and furs were factors. Eosinophilia was always present. Of 174 children treated by desensitization, diet eliminations and calcium, 32.7 per cent were cured; great relief occurred in 29.8 per cent; simple relief was obtained in 33.9 per cent, with failure in only 3.4 per cent.

Trivelli<sup>101</sup> cites seventeen cases of a condition akin to asthmatic bronchitis which occurred concurrently with a "grippal" infection; when this infection cleared so did the "asthmatic bronchitis." The symptoms occurred during an epidemic which comes on each winter in Chile. In a mining town of about 1,500, approximately 3,000 feet above sea level, the author observed these children for ten years to see if they would develop asthma. Some did and some did not, but in those who did not, some other allergic condition occurred, e.g., spring conjunctivitis, eczema or intertrigo. Ammatuna<sup>3</sup> studied allergy in Paraguay. Asthma and hay fever are most important and the main allergens are foods, fungi, and tubercle bacilli; fungi are more important in Paraguay than in other countries.

Schwartz<sup>165</sup>, in 141 patients with bronchial asthma admitted to the Long Island College Hospital from 1937 to 1941, found: seventy-seven patients developed asthma before the age of forty, and sixty-four after that age; this high percentage with late onset of asthma goes hand in hand with clinical observations that hospitalization is much more frequently necessary in those whose first asthmatic symptoms occur late in life. Sinus infection was present in thirty-two of sixty patients examined in this series; emphysema in twenty-eight of ninety-six in whom chest films were made; blood eosinophilia averaged 6.8 per cent; blood pressure was normal in 123, high in ten, low in eight; blood sugar was below 80 in five, normal in 133; diabetes was present in three cases, tuberculosis in one, and cor pulmonale in one. Gastric contents were normal in the eighteen examined cases; in fifteen patients the basal metabolic rate ranged from minus 12 to plus 19; tests for syphilis were negative in all 141 cases.

Heart studies still intrigue the student of asthma. Glaser<sup>66</sup> from his clinical experience states that "the child will undoubtedly suffer no harm even though he may have repeated attacks of severe bronchial asthma." Engelhardt and Derbes<sup>40</sup> made an electrocardiographic study in seventeen asthmatic children, five to fourteen years old, with an average duration of asthma of 4.7 years. They confirm their previous findings that uncomplicated asthma in children is not a factor in the production of heart disease. I agree wholeheartedly with these conclusions; heart disease very rarely occurs in patients unless some cardiovascular-renal disease co-exists. Cor pulmonale does occasionally occur in complicated cases, and Smeds-rud<sup>171</sup>, in a study of forty-six cases of bronchial asthma selected at random, found signs of right coronary insufficiency in fifteen cases, in five cases only during attacks. Grave symptoms, such as dilatation of the right heart, dilated conus pulmonale, cyanosis or edema, were present in six of the fifteen and in only two of the other cases. The QRS complexes were on the whole more typical of right preponderance during attacks than in free intervals. Systematic examinations should therefore be made in asthmatic patients during attacks and in free intervals, accompanied by determination of the blood pressure. Although I have not made an intensive study of tracings during and between attacks, my impression is that there is no essential difference in this regard; in a large series those whose tracings show a tendency toward right preponderance during attacks also show this in free intervals.

Fuchs, Spain and Straus<sup>60</sup>, in a study of fifty-one patients with bronchial asthma, found that (1) the amount of cholesterol in sputa ranged from 7 to 55 mg. per cent; (2) the amounts were higher in those with severe symptoms; the highest percentages were found in the infective or skin-negative type, with an average of 25 to 55 mg. per cent; in the non-infective type the amounts ranged from 7 to 25

## PROGRESS IN ALLERGY

mg.; (3) the total amount expectorated in twenty-four hours varied from 1 to 10 mg.; (4) no relation existed between the volume of sputum and the concentration of cholesterol per c.c., nor between the duration of asthma and the amount of cholesterol in the sputum; (5) those with definite bronchiectasis had higher percentages. The authors conclude, therefore, that the amount of sputum cholesterol is increased by any infectious process in the lungs, e.g., tuberculosis or bronchiectasis; it is also increased by excessive use of epinephrin and ephedrin.

Dees<sup>39</sup> studied the amount of blood serum potassium in eleven asthmatic adults, with seventeen normal controls. The fasting levels were significantly higher in asthmatic patients, as compared to those in normal individuals. There was no alteration in serum potassium level in normal asthmatic persons after subcutaneous injections of epinephrin or physiological saline solution. Nuñez<sup>132</sup> believes that 58 per cent of patients with bronchial asthma have a secondary hepatic insufficiency. His patients showed an edema of the right hand so that the fist could not be closed; this, he states, is due to hepatic disturbance related to water metabolism. He also finds a connection between biliary stasis and migraine.

Zeller<sup>213</sup> refutes the previous report that the whealing response in skin tests is inhibited under hypnosis. Two individuals, one normal, the other asthmatic, were passively sensitized with reaginic ragweed serum; positive tests were found twenty-four hours later when these sites were injected with ragweed extract. The two were then deeply hypnotized and repeated suggestions were made that the skin response would not occur, but identical wheals did occur during hypnosis when the tests were repeated. Similar results followed direct testing of ragweed-sensitive patients before and during hypnosis.

Prickman<sup>144</sup> found 207 hernias of various types in 157 asthmatic patients at the Mayo Clinic over a five-year period. Hernias were present in 2.3 to 2.8 per cent of all Clinic patients in these five years, and in 3.4 per cent of asthmatic patients. Asthma contributes not only to hernia but also to recurrence after surgical repair. Recurrences of hernias occurred in twenty-three asthmatic patients who had been operated on before coming to the Clinic. In twenty-two asthmatic patients repaired at the Clinic, recurrence occurred in six cases (27 per cent) as compared to only 6.4 per cent of 2,298 allergic and non-allergic cases in which hernias of all types were repaired at the Clinic. Prickman therefore urges control of asthma before surgery, and states that of the 157 cases herniotomy was postponed in fifty-eight and rejected entirely in fifty-one.

The relationship between bronchial asthma and pulmonary tuberculosis continues to be a live topic especially in countries where the incidence of tuberculosis is high. In my experience the two rarely occur together, and Glaser<sup>66</sup> has seen no children who have both conditions. I also agree with the answer to a query<sup>146</sup> which states, "with the exercise of ordinary precautions the physician who has asthma should be able to work in a tuberculosis hospital with no more danger than if he did not have asthma." Herbut<sup>88</sup> presents findings in a patient who had asthma, but on postmortem also had pulmonary tuberculosis, as shown histologically by the presence of granulomata throughout the walls of the smaller bronchi and bronchioles. This narrowed the diameters of the terminal bronchi, and in this case, therefore, the tuberculosis aggravated the asthmatic symptoms. Pathologic changes typical of bronchial asthma were also found in the lungs. Although asthmatoïd symptoms can occur in pulmonary tuberculosis, true bronchial asthma and tuberculosis, especially exudative, rarely co-exist, though they did occur together in the two cases mentioned.<sup>53</sup> The author says this is parallergic asthma in which the tubercle bacillus increases the total hypersensibility of the patient. Dust also acts as a parallergene and provokes attacks of asthma.

Davidson and Brock<sup>88</sup> present a case of bilateral spontaneous pneumothorax in

a sixteen-year-old girl who had asthma since the age of three years. The lesion occurred in the left chest and subsided, but four months later the right lung collapsed. One month later films revealed a bilateral pneumothorax. Silver nitrate solution was introduced into both pleural cavities to promote adhesions. Bilateral spontaneous pneumothorax is rare but Markson and Johnson<sup>116</sup> reported its occurrence in a non-allergic youngster after strenuous exercise; dyspnea and pain were severe, and fluoroscopy revealed approximately 80 per cent collapse of the right lung and about 50 per cent of the left. Dramatic relief followed removal of 3,000 c.c. of air from the right pleural cavity and about 2,000 c.c. from the left. We have had, at Wesley Memorial Hospital, Chicago, a similar case, an elderly man, with almost complete collapse of the left lung, with about 25 to 35 per cent collapse of the right. Dyspnea and some wheezing are the main symptoms. Removal of air has not been attempted because symptoms are not severe, but removal of 500 c.c. of air in another asthmatic patient with unilateral pneumothorax relieved very severe dyspnea.

Derbes, Engelhardt and Sodeman<sup>41</sup> note that pulmonary tissue may rupture; the course taken by the liberated air determines whether subcutaneous or mediastinal emphysema results, or spontaneous pneumothorax, or a combination of any of these. The blood vessels, fibrous tissue and old adhesions help determine the direction of the air. The authors discuss a man, aged forty-eight, who had sudden dyspnea and orthopnea with displacement of the heart to the opposite side, with death on the fourth day; autopsy revealed right pneumothorax with blebs at the apex of the right lung; they advise against reverse pneumothorax even though their patient died. I do not concur with this advice.

They also found eighteen cases of subcutaneous emphysema in the literature, with good prognosis, no deaths, and with recovery in all within four to fourteen days. When the escaped air is mediastinal (mediastinal emphysema) the diagnosis is apt to be confused with that of coronary occlusion, because of the substernal pain. But "the outstanding finding with air is a peculiar, loud, crackling, bubbling sound which is synchronous with the heart beat." In addition, the area of cardiac dullness may become resonant or tympanitic, and the temperature, blood pressure and white cell count are normal, as opposed to changes found in occlusion. X-ray confirms this diagnosis. When air escapes into the tissues of the neck (subcutaneous emphysema) the diagnosis is no longer in doubt, because of the pathognomonic crepitations of air in the tissues.

Schwartz<sup>166</sup> analyses twenty-five previously reported cases, with recovery, of spontaneous mediastinal and subcutaneous emphysema which have occurred in patients with bronchial asthma, and adds an additional case. A twenty-four-year-old white man was admitted to the hospital with severe dyspnea, cough and wheezing. He had eczema at two years, and repeated attacks of asthma since the age of three, with many positive reactions to foods and inhalants. Asthma recurred one week before admission, but six days later he inhaled sulfur dioxide fumes from a leaky refrigerator and symptoms were immediately intensified. No relief followed use of epinephrin, ephedrin, oxygen, or aminophyllin by intravenous route. Death seemed near. Fever, tachycardia, and wheezing were marked; there were 25,600 white cells; the electrocardiogram was normal; x-ray revealed mediastinal and subcutaneous emphysema. The next day, air crepitation was present in the neck tissues and the patient's condition improved; the emphysema spread to the entire neck and up to both ears. The wheezing disappeared on the sixth day, and the subcutaneous emphysema in nine days. He also mentions the curious crunching sound heard over the heart during systole. This complication may also occur in non-allergic conditions, e.g., influenza, pneumonia, pulmonary tuberculosis, and during labor.

## PROGRESS IN ALLERGY

Fongi and Rospide<sup>57</sup> report two cases of spontaneous subcutaneous emphysema of the supraclavicular zones and neck during asthmatic spells in young adult males. Mascheroni and his associates<sup>117</sup> also report a case which occurred in a twenty year-old female asthmatic. Their report is illustrated by five schematic drawings of the chest, with physical findings.

### DIAGNOSIS AND DIFFERENTIAL DIAGNOSIS

Mansmann<sup>114</sup> emphasizes the diagnostic value of eosinophilia in blood, nasal smears, and tissues, especially as related to nasal allergy. He examined over five thousand smears of nasal secretions and blood in the past several years, and believes this examination ranks second only to the history. One should add that eosinophilia in sputum is just as important—one can often make the diagnosis of allergy in pre-asthmatic bronchitis and in unusual dyspneic patients by finding a high percentage (up to 100 per cent) of eosinophiles in the sputum (Wright or Giemsa stain).

Sodeman<sup>112</sup> discusses problems in differential diagnosis from laryngeal, bronchial, pulmonary and other diseases. From cardiac asthma, the arm to tongue circulation time with decholin is very helpful, as he states; in bronchial asthma the time averages 10 to 15 seconds, while it may reach as high as 60 seconds in cardiac asthma. We, too, have found this test very helpful. Recently, in a doubtful case, the circulation time, with decholin, was 29 seconds; bed rest and digitalis proved very effective in removing the dyspnea. Waldbott<sup>200</sup> writes about the differential diagnosis of bronchial asthma, its association with other allergic or non-allergic conditions, and its complications. He correctly states that "when an 'asthmatic' patient is lying down he should be suspected of having some other condition." Three of his asthmatic patients gave strong positive tuberculin skin reactions; the asthma in these cases was relieved by injections of tuberculin though it had not responded to usual allergy measures. He mentions cases with rare complications—atelectasis of a whole lobe, cystic degeneration of the lungs with pneumothorax and blebs, and fracture of four ribs which occurred during an attack of asthma. I have recently seen rib fractures in such a case.

Bezaneon, Jacquelin and Celice<sup>17</sup> discuss permanent asthmatic dyspnea simulating emphysema. They state that although "emphysema" is frequently diagnosed the condition rarely exists at autopsy. Chronic dyspnea, in their opinion, may well be due merely to chronic asthma without any permanent pulmonary damage; in such cases there may be an excellent response to frequent inhalation of epinephrin and ingestion of ephedrin over long periods of time. One of their patients was relieved after dyspnea which had been steady for five years. This conception is opposite to that of Alexander who states that emphysema occurs in almost, if not all, cases of chronic asthma.

Dighiero<sup>45</sup> emphasizes the importance of bronchoscopy in differential diagnosis and in treatment; it is especially important in differentiating asthma from tracheo-bronchitis and tuberculosis. Bloomfield<sup>22</sup> discusses a new method of recording simultaneously the intrathoracic, right intracardiac and systemic pressures in man. This procedure, he states, helps in studying the circulation through the right heart when there is unusual respiratory effort or abnormalities in the pulmonary circulation.

Many non-allergic conditions have symptoms which may simulate those of bronchial asthma. Moore<sup>123</sup> stresses the frequency with which bronchogenic carcinoma may confuse, especially in the stage of partial obstruction with segmental emphysema. The wheeze may be an early symptom of carcinoma. He outlines four proved cases in all of which the diagnosis of asthma was made or suspected. Autopsy and biopsy showed carcinoma in three of the cases; in the fourth case

the diagnosis was evidenced by bronchoscopy, x-ray, and clinical findings resulting in sudden loss of weight and death. The x-ray findings are often misleading in the early stages; the clinical signs and history are much more important and if correctly used more patients could be cured by early pneumonectomy. Moore's differential table is good:

## *Carcinoma Lung*

1. Usually no allergy in patient or family.
2. Onset after forty-five, usually.
3. Cough precedes wheeze by several months.
4. Wheezing localized.
5. Diaphragm arched.
6. No eosinophilia in sputum.
7. Hemoptysis often.
8. Marked weight loss and rapid downhill course.

## *Bronchial Asthma*

1. Allergy usually present.
2. Onset before forty-five, usually.
3. Cough usually comes with or follows the wheeze.
4. Wheezing generalized.
5. Diaphragm apt to be flattened.
6. Eosinophilia usual in sputum.
7. Hemoptysis rare.
8. Weight and course about same.

Bronchoscopy should therefore be done as soon as possible. Moore quotes statistics of Overhold and Rumel<sup>135</sup> which reveal that wheezing or dyspnea occurred in 38 per cent of seventy-five cases of bronchogenic carcinoma.

"Asthma" was also suspected in a case of aneurism by Andrade.<sup>4</sup> Mendeloff<sup>120</sup> describes two patients with generalized endolymphatic carcinomatosis who had progressive dyspnea with wheezing, cough, fever and cyanosis; autopsy revealed diffuse carcinoma of the lungs in both, with primary carcinoma of the stomach in one, and aberrant pancreatic tissue in the other.

A forty-six-year-old female patient of Harkavy<sup>79</sup> with symptoms suggestive of status asthmaticus developed coma following 3 grains of seconal and 3 grains of sodium amytal. While in this condition evidence of renal insufficiency, uremia, and jaundice occurred. Autopsy: pedunculated cylindroma of the trachea, ensheathing the vagus nerve; encephalomalacia in the region of the globus pallidus; tubular degeneration of the kidneys; central necrosis of liver cords. The combined effect of bronchoconstriction (pressure on vagus) and mechanical obstruction of the bronchi was thought responsible for the status asthmaticus type of symptoms.

Bronchial adenomata which may lead to pulmonary symptoms with asthmatoïd wheeze are discussed by Nager<sup>129</sup> and Von Albertini.<sup>198</sup> The former reports seven cases and urges early bronchoscopy and removal if possible. The tumor is benign but may grow; suppuration with empyema or lung gangrene occurred in two cases. In the second series ten cases are reported, of which three were discovered at necropsy; seven of the patients were under clinical treatment, but four died.

## TREATMENT OF BRONCHIAL ASTHMA

Although all realize that best results occur in patients whose offending allergen can be avoided or overcome by hyposensitization, this year's articles dealing with these specific measures are astoundingly few. They are discussed in the recent books already mentioned but almost ignored by other writers.

Grigsby<sup>72</sup> has started something which may markedly reduce the incidence of pollen hay fever and asthma. Di-nitro-secondary-butyl-phenol (G-412) in kerosene has been sprayed at 100 pounds' pressure at a rate of 100 gallons per acre and kills all ragweed within six hours. Penta-chlor-phenol (G-410) killed 75 per cent

in twelve hours, and no further pollination occurred. Sinox in kerosene killed flower spikes, but new auxiliary buds developed. Kerosene alone merely killed ready-to-open flowers but the plants recovered and pollinated. Most of the materials used are also toxic to cultivated crops.

Hansel<sup>38</sup> advises small doses of house dust and pollen extracts. His initial dose of dust extract varies from 1:10,000,000 to 1:10,000 in adults, and from 1:10,000,000 to 1:1,000,000 in children. Dosages are increased by 0.05 c.c. until a maximum tolerance is reached; when relief is obtained there are no further increases in dosages, and the time interval between injections is increased from seven to ten, fourteen or twenty-one days. Even when injections are stopped entirely, many patients continue to be symptom free for long periods of time. Hansel also gets satisfactory results in some patients whose skin tests are negative by injecting small doses of a mold extract made from old feed-mill dust; these patients may have summer "hay fever" or asthma or vernal conjunctivitis. He makes his house dust extract from vacuum cleaner sweepings, old mattress stuffing, automobile upholstery vacuum collections, kapok, feathers, jute and ozite. Animal dander, silk, pyrethrum, tobacco or specific environmental dusts are added sparingly when indicated. He may also add some feed-mill dust.

Deissler<sup>40</sup> advises 1.0 c.c. epinephrin in oil twenty minutes prior to administration of the final dose of antigen; this will minimize or prevent a general reaction, though it will not prevent delayed shock. This is especially valuable with hormonal extracts in sensitive patients who must have the injections, e.g., insulin, liver, pituitary, androgen, estrogen, or parathyroid extracts, or substances like diodrast. Cohen and Friedman<sup>35</sup> made approximately neutral mixtures of thermostabile antibody and pollen extract, which stimulated the production of thermostabile antibody in both normal and pollen-sensitive individuals; three or four injections of the mixture were given to each of three ragweed-sensitive hay fever and asthma patients, with good clinical results and no systemic reactions. Others should try this method of treatment.

Waldbott<sup>100</sup> discusses emergencies which may come from skin tests or from injections of extracts or from other causes, e.g., syncope or from excessive effect of such an injected drug as aminophyllin or epinephrin. I disagree with his statement that "generalized reactions however occur in spite of negative scratch tests"; the only possibility for such a miscarriage is the use of scratch test material which has lost its potency, e.g. old liquid scratch materials. Those who use dry powders for scratch tests need have no fear in this regard. Waldbott rightly omits intracutaneous tests (unless very dilute) for antigens to which there is a known history of sensitivity, e.g., fish or nuts. He avoids intradermal tests in children below six years of age; they are dangerous, he states, but he says nothing about doing scratch tests in these children. Why not do scratch tests in children, at least to begin with, and why should anyone believe that initial intradermal testing is free from danger at any age<sup>134,206</sup>? Waldbott's remarks on other possible emergencies are well taken. Engelsher<sup>50</sup> disagrees with many of his statements, and is right in saying that "glycerinated extracts and powders remain stable for a much longer period than the intracutaneous allergens and furthermore are much safer to use." But I feel he is wrong in not giving intravenous injections of aminophyllin. I agree with Waldbott's "The intravenous method of administering aminophyllin is decidedly more effective and prompt in its action than the intramuscular one and therefore far too valuable to be discarded. It is safe if the precautions which are outlined in my paper are followed." Intramuscular injections of this drug, one should add, cause pain, and abscess may follow.

*Aminophyllin* continues to be one of the most effective, perhaps the most effective, therapeutic agent in the treatment of bronchial asthma. In a large series at

the office, in the hospital, and in homes, we have had but one reaction which might be called serious. A man in his sixties was given 0.25 grams (10 c.c. ampule) intravenously for severe asthma. He became pale and developed a thready pulse for a few minutes, then recovered; he may have a coexisting myocarditis, though I have not been able to prove it clinically or by electrocardiogram. Other than that, the slow administration of the drug has given remarkable results in most cases, much better and much faster than can usually be obtained by epinephrin. Goodall and Unger<sup>68</sup> read a paper, to be published, on the "Continuous Intravenous Administration of Aminophyllin in Status Asthmaticus"; several patients of the most severe type have been completely or partially relieved of their symptoms by this method, applicable to hospital practice only. Barach<sup>9</sup> suggests the rectal instillation of 10 grains of aminophyllin in 20 c.c. tap water, especially at night. Many patients say this method is less irritating than the use of aminophyllin suppositories which contain 7.5 grains; results are often rapid and excellent.

Zeller's patient<sup>212</sup>, a sufferer from asthma and rhinitis, was given an intravenous injection of 7.5 grains of aminophyllin. Her asthma was relieved and her associated marked abdominal distension (intestinal obstruction?) also disappeared. Several other episodes of abdominal distension in this patient were also promptly relieved by intravenous injections of aminophyllin. Battro and Labourt<sup>12</sup>, from Argentina, discuss respiration, and report an increase of vital capacity in 88 per cent of twenty-five asthma sufferers by intravenous injections of deriphyllin, a theophyllin preparation. Kallós and Kallós-Deffner<sup>65</sup>, in experimental work in guinea pigs, showed that aminophyllin has a decidedly greater effect on bronchial smooth muscle than on vascular structures. They used goat and eel serum and found that the former acts on smooth muscles, the latter on blood vessels. Intravenous injections of aminophyllin inhibit the toxic action of goat serum in guinea pigs but give indefinite protection or relief in eel-serum-treated animals.

*Penicillin* has recently been widely used in the treatment of all sorts of respiratory conditions, including chronic bronchial asthma and its complications, and sinusitis of all types. Administration has been both by injections and by inhalation, with variable results. Oral therapy has also been started.

Hampton and his associates<sup>77</sup> injected the drug intramuscularly into nine patients with moderate to severe asthma; the usual allergy management had failed. Five patients each received a total of 500,000 Oxford units; one received 800,000, another 1,300,000. Later, seven of these patients and two others were given penicillin intratracheally. Results were mediocre with slight improvement in four cases. A positive but transient skin reaction to a 1:100 dilution of penicillin was obtained in one patient who gave a positive reaction to penicillium-mold extract. In two cases bronchoscopic studies before and after intramuscular and intratracheal penicillin therapy were essentially the same.

Derbes and Wilson<sup>42</sup> gave 500,000 units intramuscularly to each of two patients with asthma plus bronchial infection. Great improvement followed. The dyspnea in the first patient was lessened, the temperature became normal, the appetite improved, and the predominating bacterial flora were completely changed; but the irreversible changes in the lungs characteristic of chronic intrinsic asthma were not affected. The second patient also improved, and much of the associated pneumonitis cleared. Leopold and Cooke<sup>106</sup> also obtained excellent results with cessation of asthma for four months in two patients who were given intramuscular injections of 100,000 units every twenty-four hours. One patient received 1,375,000 units and developed a serum-sickness-like reaction which lasted six days, followed by remission of symptoms. The authors treated twenty-five additional patients with asthma and conclude "It has become evident to us that penicillin is not a panacea for all cases of asthma due to infection." Penicillin is effective with staphylococcic,

## PROGRESS IN ALLERGY

clostridial, hemolytic streptococcic, anaerobic streptococcic, pneumonococcic, meningococcic and gonococcic infections. Its efficacy in infections due to Gram-negative bacilli, including Friedlander's bacillus, has not been established.

Schonwald and Deppe<sup>164</sup> treated eighty-six allergic patients of whom twenty-one were intrinsic and fifty-six mixed, with "crude" and commercial penicillin. Thirteen patients received 2,500 units two to three times a week. Asthma was present in sixty-nine of these patients, and improvement occurred in forty-one patients who had not been helped by the usual allergy management. There were very few failures. (One might remark that no one else gives such small dosages of penicillin.)

To facilitate injections of large dosages of penicillin, mixtures with various oily materials have been made so that the penicillin effect lasts longer than when given in solution. Beeswax is an ingredient in one of these mixtures, and Gay<sup>62</sup> found that crude unfiltered and filtered beeswax gave no reactions in allergic patients. He recommends a mixture of beeswax, peanut oil, and penicillin.

Reactions have occurred in non-allergic and allergic patients who have been given penicillin; urticaria and dermatitis predominate; few reactions have been serious. A young apparently non-allergic patient of Price, McNairy and White<sup>143</sup> was given 2,400,000 units of penicillin in 5 per cent dextrose in distilled water over an eight-day period. The two batches came from different manufacturers. He was clinically improved but four days after injections were stopped he was readmitted with asthma, giant urticaria, fever, and malaise. The temperature reached 105 degrees F., and the pulse 150, with wheezing, coma and cyanosis. Dramatic relief followed the intravenous administration of 1.0 c.c. epinephrin plus 50 c.c. 50 per cent dextrose. He was symptom free three days later.

The use of penicillin by inhalation was advanced by Barach and his associates<sup>10</sup> who made a concentration of 40,000 to 50,000 units per c.c., and vaporized (aerosolized) the solution through a nebulizer, e.g., Vaponefrin or DeVilbiss No. 40, attached to an oxygen tank. No irritating effects were noted in twenty patients nor in nineteen rats; mild substernal soreness occurred in three patients. The blood level of penicillin for one hour following inhalation was generally between 0.01 and 0.04 units, at times as high as 0.18. The aim of treatment is not a high blood level but a local application of penicillin to the bronchial wall. Their twenty patients had combinations of bronchial asthma, bronchiectasis, emphysema, lung abscess and fibrosis. Their results: marked improvement, apparently due to penicillin, in five patients, of whom three had bronchial asthma and became symptom free for one to two months; moderate clinical improvement in ten, of whom eight had bronchial asthma plus bronchial infections; five patients were not benefited.

Hagens, Karp and Farmer<sup>75</sup> at about the same time reported results in twenty-two patients. Urine and blood levels show that the drug is sufficiently absorbed from the lungs. Because of its local effect this method may be best for patients with pulmonary disease. Temporary improvement occurs in bronchiectasis but relapse usually follows when therapy is discontinued. Asthmatic patients who have a superimposed bronchial infection with an organism to which they may be allergic may be favorably influenced. Acute pulmonary conditions usually respond well. The method may be used advantageously in children and other patients in whom intravenous or intramuscular injections are not suitable.

Karp<sup>98</sup> has also used *streptomycin* by inhalation, with the same technique as with penicillin; in some cases the two were inhaled simultaneously. Streptomycin usually causes prompt disappearance of Gram-negative bacteria, so that inhalation of both usually leads to sterile sputum. This is extremely valuable in pre- and postoperative treatment (lobectomy or similar procedure). When these antibiotics are stopped the germs return.

Segal and Ryder<sup>167</sup> treated twenty-one patients with pneumonia, bronchiectasis,

lung abscess, and infectious bronchial asthma by inhalation of penicillin. The clinical course of six with asthma was not altered even though the penicillin-susceptible bacteria were eradicated. Blood levels of 0.028 to 0.055 were obtained; five patients with bronchiectasis were successfully treated, two before lobectomy and the other three medically. The method was very successful in three of four patients with lung abscess.

Vermilye<sup>187</sup>, in a long article on penicillin by inhalation, had excellent results in many of 200 patients. He states "aerosol penicillin has been very successful in twenty-five cases of bronchial asthma, a number of which also showed extrinsic allergies to foods, pollens or danders. While the disease may appear to be cured by a five-day course of aerosol penicillin, it is advisable to continue therapy in diminishing amounts and then in single daily or weekly prophylactic doses for a number of weeks." He believes that a chronic respiratory infection is the cause of intrinsic asthma.

An unusual side effect occurred in two patients. When aerosol penicillin was given simultaneously or within a few hours of a pollen immunization or vaccine, severe allergic reactions occurred: acute abdominal pain, urticaria, nervousness, restlessness, and angioneurotic edema; 50 mg. of demerol quickly controlled the reactions; the aerosol alone never caused the reaction. Mild urticaria also occurred in two cases. Other respiratory conditions were also successfully treated. Aerosol penicillin, he states, is just as effective as the intramuscular method and much easier to administer; it can be given in the office, at home, or in the hospital.

Seven patients with bronchiectasis were given aerosol penicillin before lobectomy by Olsen.<sup>133</sup> The quantity of sputum was sharply reduced, and the surgical risk definitely lessened. He gave prolonged daily treatment for ten hours with alternating ten-minute periods of nebulization and rest. The method also helps non-surgical bronchiectasis. Stookey and his associates<sup>180</sup> injected an average of 1,000,000 units intramuscularly or by continuous intravenous drip for eight to ten days. Their twenty-one patients had chronic bronchitis and bronchiectasis as proved by x-ray; staphylococci predominated, often associated with streptococcus viridans. There were no reactions; the colonies were reduced in number; the sputum volume was not appreciably altered. Only about 20 per cent were benefited, and recurrences usually followed when injections were stopped. Hauser and Work<sup>84</sup> obtained excellent results in chronic suppurative sinusitis and kindred conditions by injections of penicillin; they found, however, that although penicillin eliminated all evidence of suppuration in allergic rhinitis, the presence of allergy prevented a permanent cure.

Prigal and Speer<sup>145</sup> introduced a steam generator, simple and economical, for aerolization of penicillin, sulfonamides and other medicines. Steam mixed with the drug-containing vapor spouts in five to ten minutes after the current is turned on. They found effective and prolonged blood levels for both sulfadiazine and penicillin. They also obtained clinical relief in asthma by vaporizing aminophyllin by this method. Abramson and Demerec<sup>1</sup> describe a simple centrifugal fractionator of aerosols for control of particle size; the finer the mist the better the clinical results.

It is therefore difficult at this stage to decide the position of penicillin in the treatment of bronchial asthma. It frequently cures or lessens infectious complications of asthma. Good results seem obtainable both by the usual intermittent injections of penicillin and by the newly developed aerosol technique. The latter method is fairly simple, and it may more or less supplant the use of injections of penicillin in the treatment of infectious diseases of the respiratory tract. But chronic asthma, I am afraid, will still remain after the infection has been removed. Despite the optimism of some workers, I do not believe that penicillin therapy

## PROGRESS IN ALLERGY

cures asthma or other allergic diseases. I hope that more prolonged therapy, especially by inhalation, will prove that I am wrong. My own experience in a number of cases with penicillin by injection and by inhalation has shown relief of infection but very little effect on the asthma itself. One patient with chronic asthma received both penicillin and streptomycin; his sputum was cleared of both Gram-positive and Gram-negative bacteria, but wheezing and dyspnea continued.

*Sulfonamides* have of late been used less frequently. Bell's two patients<sup>14</sup> with severe bronchial asthma showed dramatic response. Both were resistant to epinephrin and both had paranasal sinusitis with streptococci predominating. Thomas, Van Ordstand, and Tomlinson<sup>187</sup> studied seventy-five patients with bronchiectasis and respiratory allergy. In twenty-three in whom sulfonamide therapy was the chief or only medication and who were observed for four months to four years, definite improvement with reduction of cough and expectoration occurred in twenty-two. Fifteen of twenty-one who received allergy management for the most part over a period of one to four and one-half years showed great improvement. In thirty-one patients both allergy and sulfonamide therapies were used; twenty-six of these were improved 25 to 100 per cent, although exacerbations occurred in all groups. Glaser<sup>66</sup> advises the use of 0.5 to 1.0 gram sulfadiazine daily to prevent respiratory infections.

Inhalation therapy is also stressed in two other papers. Wickner<sup>204</sup> outlines a method of inhaling 1 per cent epinephrin with helium and oxygen; a circle filter with rebreathing reduces expense; he used the DeVilbiss No. 40 vaporizer intimately attached to a face mask. He advocates Lockey's glycerinated epinephrin mixture; it is readily vaporized. Lockey<sup>108</sup> likes continued inhalation of 10 per cent carbon dioxide with 90 per cent oxygen with 1 per cent glycerinated epinephrin for relief of asthma. Carbon dioxide acts as an expectorant, says Lockey, quoting Holinger and his associates. One per cent epinephrin, with or without glycerin is often effective, but the role of carbon dioxide is disputed.

*Psychiatric* measures are important, even though asthma is not due to psychic factors. Mervish, in a good article from South Africa<sup>122</sup>, tells physicians, "Your attitude toward your (asthmatic) child will greatly influence the course of his complaint. You can help him considerably by having an optimistic outlook, by keeping him happy and occupied, by not allowing him to be unduly fatigued, by taking an interest in his school activities, by not drawing attention to his ill-health, and by treating him, as far as possible, not as an invalid, but as a normal child." He also emphasizes the need for psychologic studies of the parents, the child, and the school. He finds out if the parents are living together or separated, if the child is aggressive, shy or jealous, and if his school record is good. If the parents are maladjusted he instructs them to be patient, to avoid extra work for the asthmatic children, and to avoid discussing his sickness before the child. Schneider<sup>163</sup> believes too little attention is given to the influence of allergy in the cause or aggravation of juvenile emotional disturbances—the asthmatic child's fear of attacks and of possible death, his dread of allergy seasons, et cetera—any of which may increase restlessness, and cause poorer school work and weight loss. Removal of important allergens, e.g., wheat or chocolate milk, may alleviate symptoms. He discusses two children whose psychologic adjustments were markedly improved when offending allergens were removed.

Shields<sup>169</sup> discusses "nasogenic" asthma; he does not like oily drops, but does like ionization of the nasal mucosa. For asthma he urges breathing exercises, and gives detailed instructions, to be supervised by physiotherapists. Increased vital capacity may result. We Americans should make more use of breathing exercises.

X-ray treatment continues to give temporary benefit in certain cases of asthma. Dutton and Fuchlow<sup>17</sup>, in an excellent paper, realize that some asthmatic children

## PROGRESS IN ALLERGY

are not well controlled by allergy management. Some who have a sino-bronchial syndrome are benefited by four to six x-ray treatments; relief may persist up to several months or even indefinitely; the children have fewer "colds"; the x-ray findings in sinuses and chest may or may not improve. Their table of differential diagnosis:

	<i>Asthma Due to Atopy</i>	<i>Asthma Due to Sino-bronchial Syndrome</i>
1. Onset	Eczema, hay fever, asthma triad	Asthma begins with "colds"
2. Duration attacks	Paroxysmal; short duration	Gradual onset, longer duration
3. Fever	Not usual	Usual
4. Response to adrenalin	Good	Poor
5. Leukocytosis	Infrequent	Frequent—moderate to high
6. Sedimentation rate	Slow	Normal to rapid
7. Nasal smears	Eosinophilic	Neutrophilic
8. Bacteriology	Indifferent	Usually streptococcic pneumonia or staphylococcic
9. X-ray chest	Minimal changes	Striking changes
10. X-ray sinuses	Minimal changes	Striking changes
11. Seasonal incidence	Not seasonal or corresponds to pollen season	Winter or change of weather

Kaplan and Rubenfeld<sup>96</sup> report more or less relief with x-ray therapy in 72.7 per cent. When the asthma was most severe and of long duration the response to irradiation was apt to be better. Sometimes patients became temporarily worse when treatment was begun, then improved.

The relationship of bacteria to allergy continues to be a live topic. Ghosh<sup>68</sup> from India, observed hypersensitiveness to bacterial antigens after injections of bacterial vaccines in two patients. Reactions may be severe; in twelve cases tests revealed that the vaccine itself was sterile. In two cases skin tests were positive for the vaccine but negative to the media. For two to four years Stoesser<sup>178</sup> studied 214 children with histories of infections prior to onset of asthma or allergic rhinitis. Thirteen of nineteen children whose antra were punctured or irrigated had very satisfactory results. Ordinary allergy management gave good results in 66 per cent of cases, but vaccine was given to fifty-nine unimproved children. Autogenous vaccines failed in eleven children; stock vaccines gave better results in twenty-one cases, but if no improvement occurs after a few injections they should be stopped. Undenatured bacterial antigens, in twenty-seven children, beginning with 0.10 c.c. and increasing 0.10 c.c. twice a week till 0.5 c.c. or 1.0 c.c. doses, gave the best results. Remarkable improvement occurred in thirteen of these children, with fairly good results in nine, and failure in five. Stoesser therefore favors the use of undenatured antigens, and believes the response may perhaps be specific.

Toulet<sup>190</sup> favors autogenous vaccines and removal of foci of infection; in some resistant cases tuberculin helped. Turnbull<sup>192</sup> describes two patients with recurrent asthma, rhinitis and cough, complicated by recent unresolved pneumonia. Allergy management with elimination of offending foods led to relief of bronchial obstruction and to escape of the exudate from the pneumonic area. Resolution was complete in a few weeks.

Rackemann<sup>148</sup> continues his remarks on depletion in asthma. He emphasizes the value of general treatment for debility in addition to usual allergy management; he suspects that malfunction of the adrenal cortex is a factor in depletion. One patient was benefited by intramuscular injections of testosterone. One should add that a high carbohydrate, high protein diet plus frequent injections of adrenal cortex extract plus abundance of salt and salted foods are very helpful to emaciated asthmatic individuals of all ages.

Marchetti and Lavarello<sup>115</sup> treated attacks of asthma in twenty-eight cases by a

## PROGRESS IN ALLERGY

mechanical respirator in a special chamber. Patients breathed more easily, even without any medication. Ross<sup>157</sup> reports a five-year study of methods for artificial respiration, as used in coast guard stations and in fire departments of Chicago, Los Angeles, and Detroit. In 3,352 cases heart disease caused most calls, with high mortality. In 115 cases of "asthma," sixteen died; thirteen of these were not breathing at all when resuscitation was attempted; four who were not breathing recovered; ninety-eight asthmatics with impaired respiration recovered, ninety-five by use of the inhalator, three by Shafer technique plus inhalation. Comment: deaths recorded as "asthma" were not proved; some might have been due to "cardiac" asthma.

Stoesser and Booth<sup>179</sup> obtained good results by artificial fever therapy, ingestion of potassium chloride, restriction of sodium chloride, and injections of pitressin.

Bowen<sup>26</sup> comments on the management of asthmatic children. He uses nose drops very cautiously; only one in 100 children are allergic to food alone; environmental factors and infection are very important, and a balanced diet plus vitamins are essential. An exclusive management by elimination or trial diets fails in 90 per cent of cases, and Bowen emphasizes the meticulous care necessary in reducing environmental allergens, e.g., pets and house dust. He also correctly urges the preliminary use of scratch tests; intradermal tests are then to be done, if necessary. Goodman<sup>69</sup> discusses treatment of status asthmaticus in hospital practice.

Within the past year the "Gay" treatment for asthma<sup>147</sup> has become almost a fad. Doctor Gay of Biloxi, Miss., gives asthmatic patients a mixture of Fowler's solution, potassium iodide, tincture of digitalis, and phenobarbital, in varying amounts, depending on the weight of the patient. He also adds calcium lactate and nose drops. Many patients have been benefited. The relief has usually been temporary, and may be due to (1) change of environment, (2) the action of the drugs, and/or (3) the psychologic aspects of a change in doctor and medicine. This reviewer has tried this regime in about ten or fifteen patients who have chronic asthma; good, though temporary results, were obtained in three cases—one patient needed no epinephrin for over three months. Arsenic and potassium iodide have long been used in the treatment of asthma; the addition of digitalis, of course, is not warranted unless there is evidence of cardiac decompensation or fibrillation. One must guard against exfoliative dermatitis or other possible results of arsenic.

Exfoliative dermatitis followed ingestion of 16 mg. ephedrin sulfate by a fourteen-year-old asthmatic patient of Engelsher.<sup>51</sup> Kallós and Kallós-Deffner<sup>94</sup> have a new epinephrin preparation (adrenalin retard) which is able to arrest experimentally produced asthma, usually fatal. Jefferson<sup>93</sup> gave intramuscular injections of ether in oil to five patients. The sterile mixture of mineral oil and anesthesia ether is kept in the Provident Hospital emergency room. Injections of 2 to 5 c.c. were given daily to animals, without ill effects, and in 2.0 or 3.0 c.c. doses in the human it has relieved many attacks of asthma. The patients taste the ether almost immediately, and they feel a stinging sensation which quickly disappears. There have been no abscesses or other local trouble. Some success in the treatment of asthma has followed administration of oil of roses<sup>2</sup>, guaco<sup>110</sup>, and acetylcholin.<sup>65</sup>

Hartman<sup>83</sup> favors the parenteral use of butanefrine in asthma. In 1:500 solution it is as effective as 1:1,000 epinephrin hypodermically in relieving asthma of purely reflex and extrinsic origin. Butanefrine is less effective when bronchial infection is present; but it is better than epinephrin in that it does not cause angina, nausea or pressor effects, and tremor and nervousness are less frequent. It may therefore be safer when a cardiac factor may be present. The average subcutaneous dose is 1 mg. per 45 kgm. body weight.

Demerol is fairly effective in asthmatic attacks, and preferable to opiates. In

addition to the reports previously listed (1), Batterman<sup>11</sup>, Douthwaite<sup>16</sup>, Barach<sup>8</sup>, and Hepburn<sup>87</sup> state that demerol is valuable and without morphine's danger. Hobbs<sup>90</sup>, however, had a patient who developed severe confusion after twenty-six injections of 50 mg. each in the course of three days. Glaser<sup>66</sup> gives 1.5 mg. per kgm., often in the same syringe with epinephrin.

The value of ethylene disulfonate is very doubtful. Kurland and Bubert<sup>102</sup> injected twelve patients with chronic asthma over a period of seventeen weeks. No relief was obtained in five, while three patients were slightly improved and two definitely improved. They conclude that the claims made by the original workers are excessive and the drug has little if any therapeutic value. Archibald<sup>7</sup>, in a study of forty-five children for six months to three years, found that one or two injections of distilled water gave about as much temporary relief, if any, as did one or two injections of the drug itself.

The so-called "antihistaminic" drugs have recently received much publicity. Benadryl is now on the market in 50 mg. capsules and as an elixir, with 10 mg. to the dram. Pyribenzamine is also now available. These drugs are of little use in the treatment of bronchial asthma. They are excellent, however, for relief of pruritus, urticaria, angioneurotic edema, and serum sickness; they also lessen the nasal congestion of allergic rhinitis and hay fever. They are not specific, and though they do lessen or prevent histamin shock in animals there is no proof that histamin causes allergic conditions in man. Among recent articles are those of Parrot<sup>139</sup>, Loew, Kaiser and Moore<sup>109</sup>, a symposium from the Mayo Clinic<sup>185</sup>, Feinberg and Friedlaender<sup>54</sup>, and on "Antagonists of Histamine."<sup>137</sup>

Lobectomy continues to increase in favor in the treatment of bronchiectasis, with or without associated asthma. Head<sup>85</sup> has had remarkable results; he recently removed left lower lobes from two of my patients, one of whom also had hay fever and asthma. When allergy coexists it is wise to keep the patient in an "asthma" room in the hospital before and after lobectomy. The use of penicillin has lowered the mortality so that surgery is more readily advised. Carlton and Adams<sup>30</sup>, in a report on lung resection in pulmonary suppurative disease, had two deaths in forty-five operations made on thirty-six patients with bronchiectasis, twenty of which were bilateral.

Other papers have appeared. Castilla<sup>31</sup> writes on the social problems of asthma, and urges early treatment in children. Stanley<sup>176</sup> divides asthma into seven groups, according to severity; "this theory suggests that an inflammatory focus may give rise to something (leucotoxin) which is transferred, probably by the blood stream, independently of the transfer of any actual organisms or bacterial toxin." His theory is new; his treatment is not. L. Gay<sup>61</sup>, in scholarly language, acknowledges the debt that medicine, including allergy, owes to the exact sciences such as chemistry and physics. He contributes this: "Respiratory distress of a violent type frequently results from a dust hazard little suspected by the average physician, and certainly not suspected by the engineer who originally designed the pipeless furnace method of house heating. It consists of one large central hall register through which hot air passes and distributes both dust and imperceptible gas from the first floor to the attic. Unfortunately its popularity because of its cheapness has been widespread throughout the farming districts and small country towns. It is one of the common causes of winter asthma in both the child and the adult and must be looked upon as a serious health hazard. Relief of the asthmatic tendency is obtained after the removal of the 'hot-air' system of heating."

A physician was found guilty of prescribing morphin and ephedrin on numerous occasions to an addict who fraudulently claimed he had asthma.<sup>119</sup> In Argentina some physicians are medicolegal experts and are assigned by judges in occupational disease lawsuits. Roimiser<sup>155</sup> describes a patient who developed asthma after

## PROGRESS IN ALLERGY

working in a leather and jute factory; an extract of floor dust was very positive. Zanehi and Sivori<sup>209</sup> discuss four medicolegal cases which involved a worker in a cigarette factory who developed allergic rhinitis and asthma, with positive skin and transfer reactions to tobacco-blend; a clothing store worker who became asthmatic and gave positive reactions for silk, wool and cotton; a baker with rhinitis and asthma from flour, with positive skin tests for wheat and rye; and a wheat-mill worker who developed asthma and gave positive tests for grain mill dust and for parasites in this dust.

The new Allergy Unit at the University of Illinois College of Medicine is teaching a group of students fundamental and clinical allergy as well as those sciences which are of aid in allergy. This undertaking is to be commended.<sup>130</sup> Also to be congratulated is the National Home for Jewish Children in Denver<sup>131</sup> which has "for the past five years been caring for underprivileged children suffering from acute bronchial asthma and other refractory upper respiratory diseases." The Home is exceptionally well managed, and almost every child, no matter how chronic or how severe its asthma was, has been benefited, some to a remarkable extent. Avoidance of house dust, as in the Stockholm experiment, must be a large factor, but removal from parents is also important in some cases.

A number of other papers have appeared, mostly of a general nature. Among the authors are Müller<sup>128</sup>, Mountain<sup>127</sup>, King<sup>100</sup>, Graham<sup>70</sup>, Friedlaender<sup>59</sup>, and Walton.<sup>201</sup> Forman<sup>58</sup> states, "Although the pathologic basis of asthma was once supposed to be spasm, it is a curious fact that spasm has never been demonstrated in any case studied by bronchoscopy."

Harley<sup>81</sup> humorously observes that "the study of allergy continues to be an intriguing confusion of conflicting theories and rich promises." He also says that "the old Persian proverb still applies: when you go to a general practitioner he tries to treat what you've got, but when you go to a specialist you've got what he treats!"

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# News Items

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## Introduction to Pollen Analysis

A new course designed to present the fundamental principles and techniques involved in pollen research is being conducted by Dr. A. O. Dahl, Department of Botany, University of Minnesota. It has been arranged as a three credit, 10 weeks' lecture, laboratory and demonstration course offered during the spring quarter for Senior College undergraduate, graduate and unclassified students who possess a sufficient background and interest to study this more or less specialized phase of botany. The course prerequisite is placed on this basis rather than arbitrarily listing a series of prerequisite courses which may not, feasibly, be part of the students' curriculum.

The course opens with a brief survey of basic pollen structure as seen from a developmental (ontogenetic) point of view. This is followed by a more or less intensive study of the comparative morphology of various kinds of pollen grains, during which experience in identifying pollens as well as in preparing reference slides is gained. Ability to identify various kinds of pollen is checked periodically by means of "practical" demonstration examinations. Students also expose and analyze their own atmospheric slides. Exercises on pollen certification are included.

The various applications of pollen research to the fields of allergy, ecology, and phylogeny are briefly considered.

Since the course is a specialized one and consequently one of limited size, the emphasis in the latter part of the course is more or less related to the special interests of the students—those who are particularly interested in allergy would continue in that phase of pollen study, whereas those who are more interested in the phylogenetic (or other) aspects would be concerned with techniques particularly suited to such fields.

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## A Proposed Section on Allergy in the American Medical Association

On Thursday, July 4, a committee representing both allergy societies appeared before the Reference Committee on Sections and Section Work of the American Medical Association. Dr. George Piness of Los Angeles informed officers of the College that a petition was being presented to the above committee requesting the formation of a Section on Allergy in the American Medical Association. Since the College was holding its meeting at San Francisco, members of the Board of Regents of the College, who are Active Fellows of both societies, joined with Doctor Piness when appearing before the Committee, requesting that they give serious consideration to the formation of such a Section.

It was pointed out to members of the Committee that allergy is now an accepted specialty, that through the years it has proven its value and now plays an important part in medicine and is equally as important a specialty as any other in the field of medical specialties, and that recognition by the American Board of Internal Medicine as a subspecialty is evidence of its importance.

A report of the Reference Committee on Sections and Section Work (J.A.M.A., July 20, page 1000) concludes, "After consideration of the information as presented by the reports of the Academy and the American College of Allergists, the Reference Committee recommends that the question be referred to the Council on Scientific Assembly for study and recommendation."

This subject is very important, and all men interested should urge the House of Delegates of the American Medical Association from their respective states to form such a Section. The names of these delegates will be sent on request.

## NEWS ITEMS

### Latin American Edition of Annals of Allergy

What was formerly known as the "Spanish Supplement" of the ANNALS OF ALLERGY, which contains comprehensive abstracts in Spanish of all of the scientific articles in each issue of the ANNALS, under the direction of Dr. G. Estrada de la Riva, Havana, Cuba, is now called "Latin American Edition of Annals of Allergy" and has been enlarged to 24 pages. It also contains the translations of the Progress Notes or annual reviews of the literature of the various phases of allergy.

The Spanish Supplement has been mailed to all the Latin speaking allergists and physicians interested in allergy without charge as one of the graduate and undergraduate features established by the College.

The new Latin American Edition is now being published in Havana and is accepting advertisements of American Council-accepted products and those approved in other countries. These will be limited to enough to pay for the cost of the publication. The first issue has an attractive cover with the outside back page carrying an advertisement of the Marcelle Products Company, Inc., and the inside back page an advertisement of the Associated Medicinal Specialties, S.A.

In each edition, Dr. Estrada de la Riva is introducing the various officers of the College to the Latin American readers. Dr. Estrada de la Riva states that there has been a great demand for the new Latin American Edition.

Allergy can no longer be nationalistic, and we have every reason to believe that this gesture on the part of the College to eliminate isolationism is a step in the right direction.

The officers of the College wish to take this opportunity to express their sincere gratitude to Dr. Estrada de la Riva for his great contribution in making these advances.

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We are pleased to announce the return from service of the following members of the College and their present locations: Major Ralph I. Alford, 83 Park Street, Montclair, New Jersey; Captain Kenneth R. Andrews, 331 West Second Street, Lexington, Kentucky; Captain Donald L. Arey, 304 Linden Drive, Danville, Virginia; Lt. Benjamin B. Burrill, Jr., 85 Maolis Avenue, Bloomfield, New Jersey; Captain Morris J. Chernack, 1749 Grand Concourse, Bronx, New York; Captain Bernard Dickstein, 201 Dryden Building, Flint, Michigan; Col. Edwin G. Faber, 700 South Bois d'Arc, Tyler, Texas; Captain Morris J. Hoffman, Medical Arts Building, 715 Lake Street, Oak Park, Illinois; Captain I. Leonard Levin, 1427 South Lakeview Boulevard, Lorain, Ohio; Major Harry P. Loomer, Hotel Elmar, 235 South Hope, Los Angeles, California; Captain Benjamin Nozik, 10535 Carnegie Avenue, Cleveland, Ohio; Captain Harold Rand, 63 Tinafly Road, Englewood, New Jersey; Lt. Maury D. Sanger, 285 New York Avenue, Brooklyn 16, New York; Captain William B. Steen, 110 South Scott Street, Tucson, Arizona.

---

It is interesting to learn through Dr. Mieczyslaw Obtulowicz, Krakow, Poland, privat-docent of Dermatology and Venerology at the University of Krakow, who is now interested in organizing a Polish Allergy Society for the purpose of joining the International Association, that Poland has a well organized lay Society for the Prevention of Asthma. There are a few physicians interested in this public relations program which is chiefly for the purpose of securing financial aid for asthma sufferers, the placing of asthmatic children in resorts or homes where there are climatic advantages and to arouse the interest of laymen and physicians in allergy. Dr. Obtulowicz reports that following the recent world war, asthma has increased markedly in Poland, the chief contributing factors being the marked undernutrition

*(Continued on Page 338)*

# BOOK REVIEWS

WHAT YOU DON'T KNOW MAY HURT YOU. Jack A. Rudolph, M. D., and Howard N. Rose, B.A., 138 pages. Illustrated. Philadelphia: Dorrance & Company, 1946.

This small primer has succeeded very well in describing allergy to the laity. The language is simple, the text is humorous yet instructive. There are many case reports which discuss allergies to various foods and substances. Most of these are well told. A few seem a bit sensational, but the average lay reader probably does not like to be educated and bored at the same time. The last of the six chapters contains the definitions and some scientific information; the first five chapters consist chiefly of case reports.

L. U.

ALERGIA. LAS ENFERMEDADES ALERGICAS. DIAGNOSTICO Y TRATAMIENTO. By Julio A. Moretti and Luis A. Martinez Bula. 207 pages. Montevideo, Uruguay: Libreros Editores A. Monteverde y Cia ("Palacio del Libro"—25 de Mayo 577), 1944.

The authors are physicians who care for allergic patients at the Pereyra Rossell Hospital in Montevideo. They give credit to their teacher, Dr. Jaime Levinton, Allergist of the Rawson Hospital, Buenos Aires, who studied in the United States. In Chapter I they discuss the importance of allergy in all specialties, together with the history of allergy and anaphylaxis, definition of terms, and a list of allergens; also a brief summary of reagins, antibodies and theories of allergic reactions, including histamine and physiochemical cell change. Classifications are discussed in Chapter II, with special stress on fungi as factors, together with the subjects of allergy and immunity, and of allergic toxemia. In Chapter III the authors describe their allergy service in the hospital. They average 70 to 90 skin tests, all intradermal. They manufacture their own food, inhalant and fungi extracts, and report no trouble with these and no constitutional reactions. They do not test for nitrogen. In their experience of more than 50,000 intradermal tests they pay attention only to real positive reactions. Their food extracts are prepared from foods as they are actually eaten; e.g., raw lettuce or cooked meats.

Respiratory allergy is classified after Urbach. They stress the frequency of hydatid cysts of the lungs, often associated with urticaria.\* Many inhabitants, especially gauchos, eat meat which is barely cooked, hence hydatid cysts are common in Argentina and Uruguay; the cysts may also occur in the liver, and "asthma" sometimes disappears when cysts are evacuated. Other chapters deal with Digestive Allergy, Food Allergy (they test for twenty foods), Dermatologic Allergy, including atopic dermatitis, urticaria, angioneurotic edema, and contact dermatitis, Purpuras, and Allergy of the Nervous System, including migraine and epilepsy.

The book is based on a study of 217 allergic cases, of which 121 are respiratory, 43 dermatologic, 2 purpuric, 19 digestive, 18 nervous, and 7 unclassified. Eighty-seven of 105 asthmatic patients had perennial symptoms. The results of treatment in asthma were good, with 37 per cent obtaining total relief, and with only 19 per cent failures. Food allergy is most important, with only 5 per cent due to pollen, despite extensive pollen surveys. Inhalants and molds are important and bacteria play a part.

The latter part of the book discusses the literature (no personal experience) on allergy of the cardiovascular endocrine, genitourinary and ophthalmic systems.

The book contains a great deal of useful information.

L. U.

\*The reviewer is indebted for help in translation to Dr. Carlos Tanturi of Buenos Aires who wrote a thesis in 1930 in which he reported 1,000 cases of hydatid disease: the Casoni skin test is accurate in 90 per cent of cases; eosinophilia (5 to 60 per cent) in about 65 per cent; complement-fixation reaction positive in 39 per cent. He also found marked local eosinophilia in wheals removed from skin test sites.

## NEWS ITEMS

(Continued from Page 336)

prevalent in the country and the intense exposure to rubble dust from the mass destruction of cities.

Books which are badly needed by the Skin Diseases' Section of the Jagellonian University of Krakow, c/o M. Obtulowiez, M.D., are:

Clendening-Hashinger: Methods of Treatment by L. Clendening

The Care of the Aged by Malford W. Thewlis

Physiology in Modern Medicine by Macleod

Chemotherapy of Gonococcal Infections by Herrold

Handbook of Communicable Diseases by F. H. Top

Synopsis of Clinical Syphilis by Howles

Synopsis of Allergy by Alexander

Synopsis of Applied Pathological Chemistry by Andes-Eaten

Synopsis of Clinical Laboratory Methods by Bray

Histologic Technic by Krajian

Methods for Diagnostic Bacteriology by Schaub-Foley

Introduction to Biochemistry by Fearon

Laboratory Diagnosis of Syphilis by Eagle

Introduction to Dermatology by Suttan

Diagnosis and Treatment of Diseases of the Hair by McCarthy

Medical Mycology by Dodge

Histopathology of Skin Diseases by McCarthy

The Mask of Sanity by Cleekley.



### BRONCHIAL ASTHMA • HAY FEVER • URTICARIA

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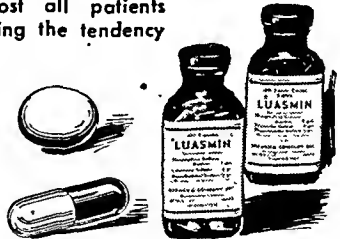
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A LUASMIN capsule, administered as needed, and supplemented with an enteric coated tablet makes it possible for almost all patients to enjoy the benefits of a full night's sleep thus minimizing the tendency of recurrence of symptoms on the following day.

Each capsule or enteric coated tablet contains:

Theophylline Sodium Acetate	3 grains
Ephedrine Sulfate	1/2 grain
Phenobarbital Sodium	1/2 grain

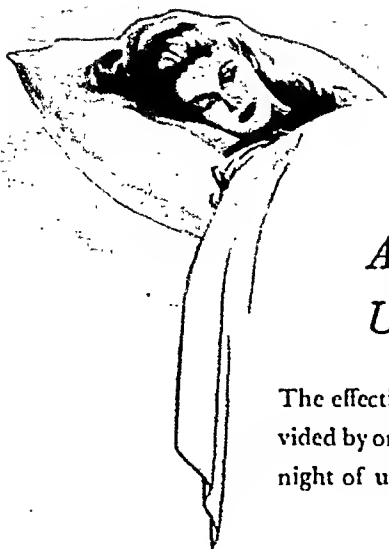
Half formula capsules and tablets are also available for children, or for adults when symptoms are mild.  
Write for descriptive literature and professional samples.



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EST. 1852

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The effective prophylaxis of nocturnal attacks of asthma provided by one Adnephryn capsule taken at bedtime ensures a full night of uninterrupted sleep, except in the most severe cases.

# Adnephryn Capsules

*To Relieve Bronchial Spasm*

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**DOSAGE:** Adults—one capsule three or four times daily. Prophylactically—one capsule just prior to anticipated attacks; one capsule at bedtime controls nocturnal attacks.

**SUPPLIED** in bottles of 50 capsules.

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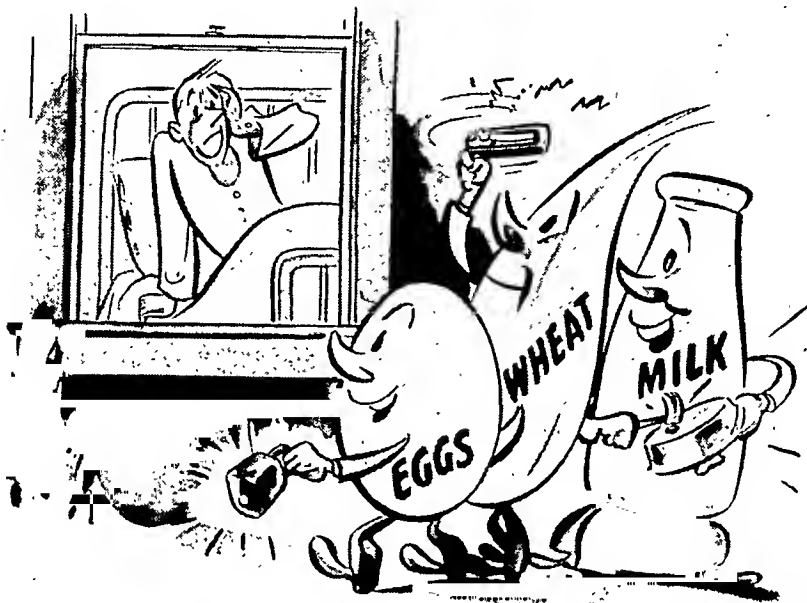
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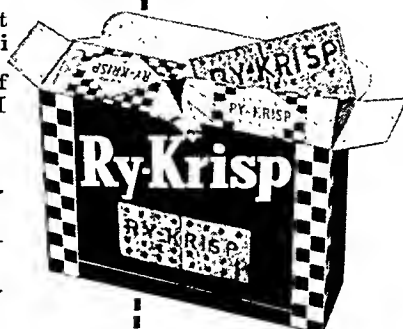
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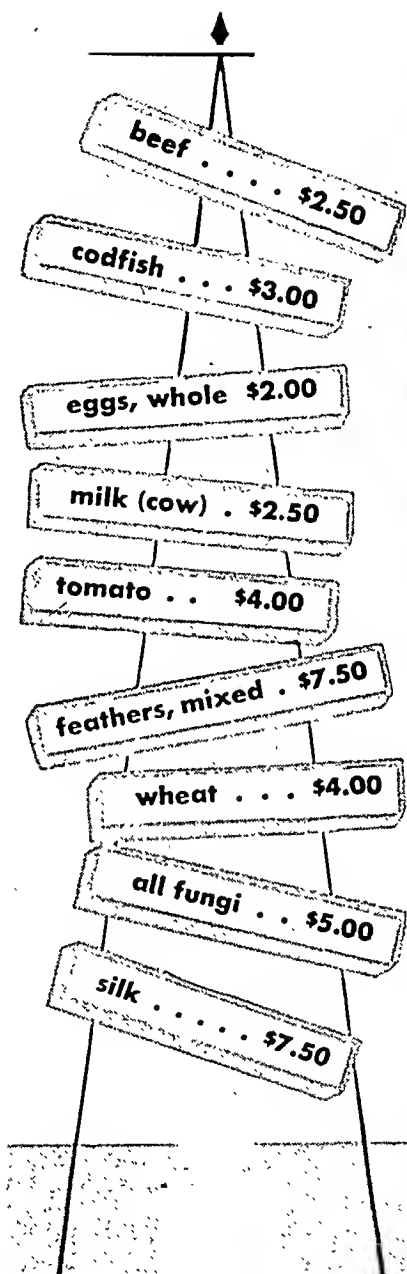
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BOTTLES**

BOTH ALULOTIONS have a unique adsorptive base of kaolin and aluminum hydroxide which mixes with the vesicular exudate and dries to form a protective coating. This *fixing* action prevents further spread of the infection.



**6 FL. DR. AND  
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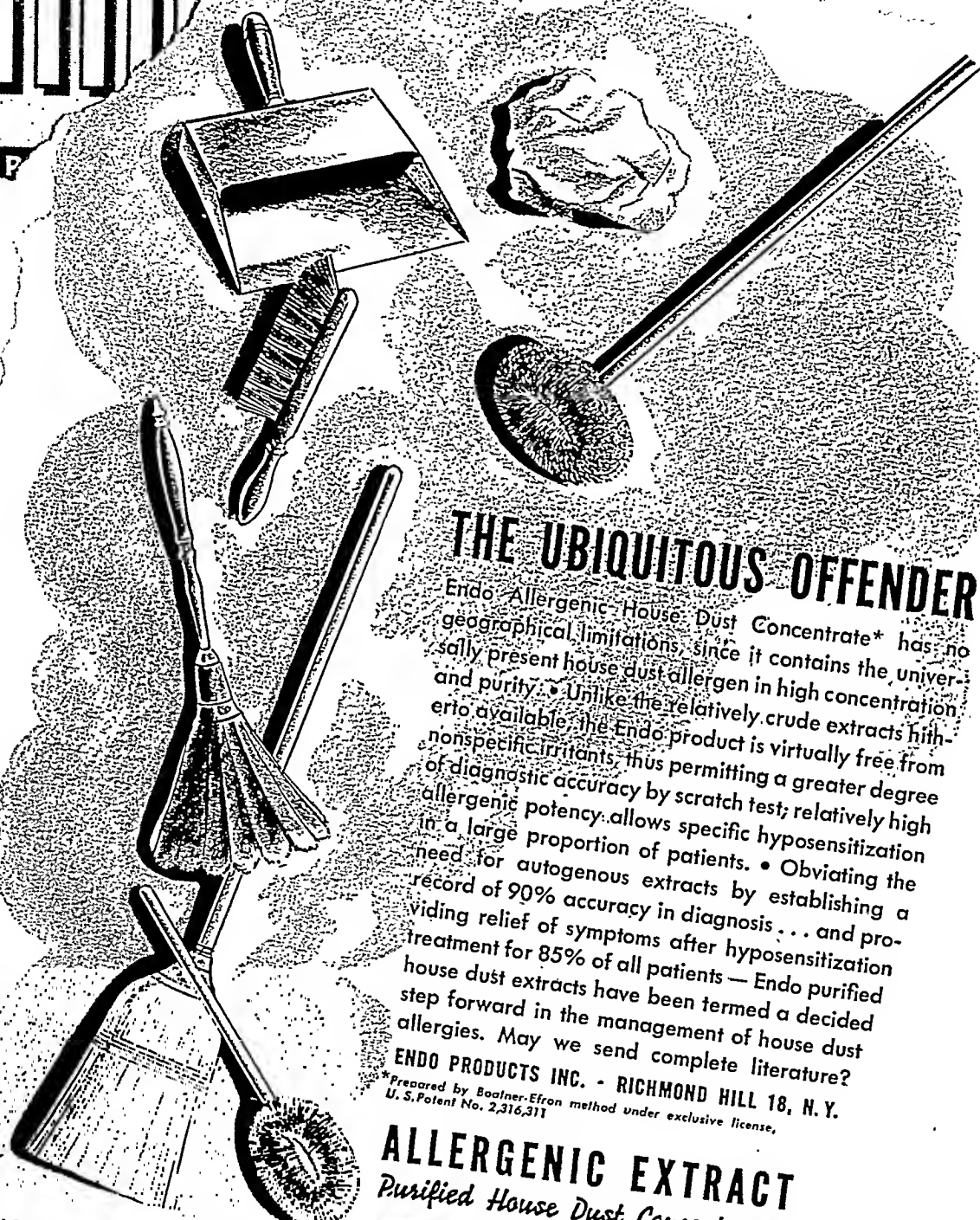
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September-October  
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Volume 4, Number 5

Published Bimonthly



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# WHEN MILK BECOMES "FORBIDDEN FOOD"

## SYMPTOMS

Persistent G.I. disturbances  
eczema, allergic rhinitis

## DIAGNOSIS

Infant shows obvious  
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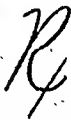
## TREATMENT

Eliminate milk from diet  
Replace with suitable hypoallergenic substitute  
(Mull-Soy)

## COMPARATIVE COMPOSITION

1 Part Mull-Soy 1 Part Water	Average Whole Cow's Milk
3.1% . . . . Protein . . . .	3.3%
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87.2% . . . . Water . . .	87.3%

Each provides 20 calories per fluid ounce



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# ANNALS *of* ALLERGY

Official Journal of the  
American College of Allergists

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St. Louis 3, Missouri

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401 La Salle Medical Bldg.  
Minneapolis 2, Minnesota

Annals of Allergy is published bimonthly by the American College of Allergists. The contents of the journal consist of contributions in the field of diseases of allergy, book reviews, a current bibliography, editorials, case reports, new suggestions, questions and answers, news items and matters concerning the affairs of the American College of Allergists.

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Manuscripts must be typewritten, double spaced, with good margins, on one side of the paper only. Please submit two copies of your manuscript.

Authors are requested to abstract their articles, limiting the abstract to 150 words or not more than 200, for inclusion in Biological Abstracts, published by the University of Pennsylvania. Send abstract with original manuscript.

All material for the current issue must be in the hands of the Editor by the fifteenth of the month preceding date of issue.

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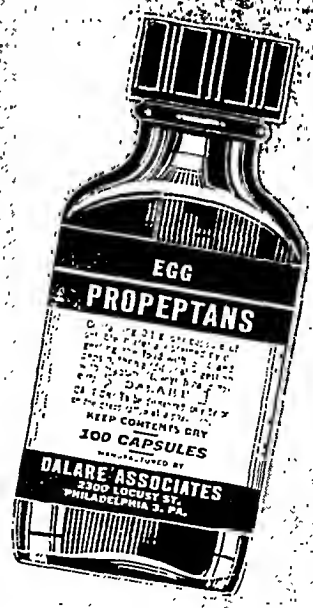
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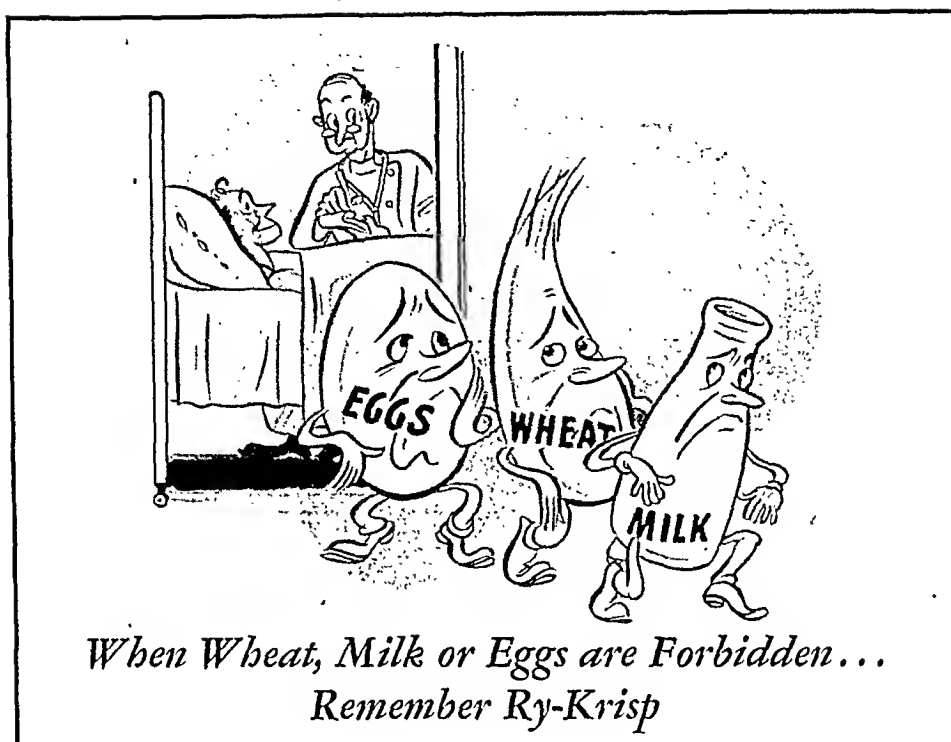
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## *Contents for September-October, 1946*

THE INTEGRATION AND DIFFERENTIATION OF ALLERGIC PHENOMENA. <i>Professor Robert R. Doerr, Basel, Switzerland.....</i>	339
BOTANICAL SURVEY OF SOUTHERN CALIFORNIA. <i>Willard S. Small, M.D., F.A.C.A., and Grace M. Small, Pasadena, California..</i>	352
CHROMIDROSIS ASSOCIATED WITH RAGWEED HYPOSENSITIZATION. <i>Helen C. Hayden, M.D., F.A.C.A., Decatur, Illinois .....</i>	372
ALLERGIC CAUSES OF PRURITUS ANI. <i>F. R. Rugeley, M.D., Wharton, Texas .....</i>	374
THE QUANTITATIVE LEPROMIN TEST IN LEPROSY. <i>M. Salazar Mallen, M.D., F.A.C.A., and L. Rosas Prieto, Ph.D., Mexico City</i>	379
CONTACT DERMATITIS FROM JAPANESE RIFLES. <i>Lt. Frank Hinman, Jr., MC, USNR .....</i>	384
ALLERGIE. <i>C. Von Pirquet, Vienna, Austria .....</i>	388
BRONCHIAL ASTHMA IN THE YOUNG MALE ADULT. A Study of Fifty Patients Returned from the Tropics for Bronchial Asthma, as Compared to Fifty Asthmatics Stationed in the United States. <i>Frank L. Rosen, M.D., Newark, N. J. ....</i>	391
THE TREATMENT OF PENICILLIN URTICARIA WITH NICOTINIC ACID. <i>W. C. Service, M.D., F.A.C.A., Colorado Springs, Colorado .....</i>	397
DEPARTMENT OF CLINICAL PATHOLOGY AND LABORATORY PROCEDURES: Rapid Darkfield Technique for Examining Sputum. <i>L. O. Dutton, M.D., F.A.C.A., El Paso, Texas .....</i>	399
EDITORIAL:  A Brief Critique of the Newer Anti-Histaminic Drugs .....	400
NEWS ITEMS .....	404
BOOK REVIEWS .....	407

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## THE INTEGRATION AND DIFFERENTIATION OF ALLERGIC PHENOMENA

PROFESSOR ROBERT R. DOERR  
Basel, Switzerland

I WISH to thank the members of the American College of Allergists for the invitation to their second annual convention. The recognition you have given my work in the fields of anaphylaxis and allergy has made me most happy, although I feel that, if deserved, it is only to a modest extent. I am especially pleased that, in these later years of my life, the generosity of the College has enabled me to visit the United States, a country toward which the hopes of all freedom-loving peoples are directed.

I am not certain that I am entitled to speak authoritatively before you. You are in possession of an enormous and constantly increasing amount of knowledge concerning allergic phenomena. My investigative work belongs to the past, and is based not so much upon my own medical experience, as upon theoretical considerations. And also, we have had no access to the American literature of the last five years, and only a few of the journals have recently been available to me. You must forgive me if I quote data not generally accepted or else denied. Within these limitations, I would like to sketch briefly, "The Integration and Differentiation of Allergic Phenomena."

In 1929, in the preface to the first issue of the *Journal of Allergy*, the editor stated that the word "allergy" lacked any generally accepted scientific meaning, but that it had been adopted chiefly by clinicians to designate specific hypersensitivities. This statement implied two important criteria, first that the reactions could be caused by specific, that is, definite, substances, and second that it possessed a pathological character, although this latter connotation is not adequately characterized

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An address given at the second annual convention of the American College of Allergists, San Francisco, California, June, 1946, as translated and presented by Ethan Allan Brown.

by the term "hypersensitivity." The allergic individual does not react, in a quantitative sense, more than the normal individual; he reacts differently, quite differently. He is not more sensitive but qualitatively sensitive in the true meaning of the word "allergic."

This observation and its implications incorporate the entire problem. There are indeed only two questions which require answer: Why are allergic reactions specific, and why do they manifest themselves in functional and structural damage to tissue cells?

Any certain knowledge we have regarding these problems stems directly from an analysis of experimental anaphylaxis. This is especially true of those experiments which are concerned with passive transmission of the anaphylactic state from actively sensitized to normal animals by means of serum injections. Here it is not necessary to search for the cell-damaging agent as part of the injected antigen, but rather in the reaction produced by the antigen and the antibody in the actively sensitized animal. Within these limits must lie all attempts to clarify the mechanisms of allergic phenomena.

In this regard, I must quote Coca<sup>6,7</sup>, who, considering the sharply manifested specificity of non-reaginic food allergy, recognizes as a cause "a specific antibody-like mechanism."

It seems to me, that the present separation of anaphylaxis from the greater bulk of allergic phenomena is a disadvantage since many of the gaps which would have justified such a separation are now being bridged. In almost all forms of allergy, specificity can be taken back to previous sensitization and also passive transfer has been demonstrated not only by the Prausnitz-Kuestner technique, but also by the transfer of whole blood from allergic to normal individuals. This fundamental and suggestive work was initiated, in 1919, by Ramirez<sup>54</sup> and in 1941, by Lovelless<sup>42</sup> whose systematic experiments demonstrate convincing conclusions.

Integration and differentiation, as in mathematics, are also in the biological sciences equally important operations, each supplementing the other. The investigation of all the related phenomena by either method may lead to valuable results, although neither technique gives us a basic understanding of either naturally occurring or experimentally induced phenomena. The ultimate objective may well be obtained by one approach or the other. In my opinion, one cannot, at the moment, foretell which will be more profitable.

If we view anaphylaxis as a central phenomenon about which must be grouped all forms of specific sensitivity, casually related, the significance of such relationships must be substantially limited by two lacunae in our knowledge. First, in spite of an enormous amount of work, our knowledge of the exact mechanism of the anaphylactic reaction is by no means complete. Originally, we thought that we had to have an antigen-antibody reaction presumably associated with an immune-body precipitation. But this is by no means certain. The recent work of

Kabat and Landow<sup>24</sup> would suggest that the anaphylactic reaction may be, as described by Friedberger, a precipitation, *in vivo*, in the zone of surplus antigen and under certain quantitative conditions, in which, *in vitro*, no such precipitation occurs, the antigen-antibody complex remaining in solution. The reason for the fact that under these circumstances the intensity of the anaphylactic reaction reaches so great a height is certainly not apparent. In the experiments with passive anaphylaxis, the free antibody and the antigen in solution react within the experimental animal. How are we to relate the reaction as seen generally or humorally with that seen locally, as in the shock that occurs in the smooth muscle of a test guinea pig?

It is true that we have learned from the Schultze-Dale<sup>12</sup> reaction that the uterus of the normal guinea pig can be sensitized, *in vitro*, by contact with immune serum containing antibodies. We explain this by saying that the antibody is bound by the horn of the uterus. But do we really understand what this process represents? According to the current conception, the antibodies are immune-globulins differentiated from the normal globulins of blood plasma by their affinity for an antigen, but this antigen, however, is not present in the tissues of the wall of the uterus of the normal guinea pig. In any case, there is no certainty as to whether or not the antigen-antibody reaction itself is sufficient to produce the symptoms or whether the presence of a mediator of a dynamically uniform, toxic nature is required.

It might well have been considered that a toxic factor of this type, whose action becomes apparent when the shocking dose of an antigen is injected, could be due to a rapid parenteral proteolysis of the injected material, except for the experiments of Tomsik and Kurotschkin<sup>64</sup>, who produced such anaphylactic shock by the injection of non-protein haptens, that is, by bacterial polysaccharides. This concept may be replaced by the hypothesis that histamine may be the causative substance, but this theory cannot in its turn be considered a definite and final solution to our problem. In recent reviews, Rocha e Silva<sup>57</sup> and also Dragstedt have had to concede that the question regarding the relationship between the antigen-antibody reaction and the release of histamine cannot, at present, be answered. Dragstedt adds that, in view of all of the phenomena regarded as anaphylactic, it cannot be decided whether the release of histamine, or histamine-like substances, considering their life-threatening character, has little or great significance in the pathogenesis of the symptoms observed. These reservations of Dragstedt<sup>16,17</sup> stem directly from the experimental data demonstrating the differences in the anaphylactic reactions seen in different species of animals, as far as the histamine content of the blood in anaphylactic shock is concerned. This histamine content, as we know, is not increased in the rabbit, in the horse, and in the calf, but rather is markedly decreased, as shown by Rose and Weil<sup>55</sup> and by Code and Hester.<sup>8</sup>

The uterus of the sensitized guinea pig reacts to contact with the antigen in the Schultze-Dale technique with a histamine-like contraction. As shown by Albert and Walzer<sup>1</sup> this cannot be reproduced with the uterine muscles of the *Macacus rhesus* monkey. And if the experiments of Tuft<sup>65</sup> are decisive it cannot be reproduced with strips taken from the uterine wall of women actively sensitized to horse serum. In any case, the behavior of the smooth muscle of the guinea pig in the Schultze-Dale reaction is not completely clear.

In Dale's experiments, in order to sensitize a normal uterus, a one to five hour infusion of the muscle tissue with antiserum is necessary. According to the experiments of Kulka<sup>30,31</sup> the mere dipping of the horn of the uterus into a solution of antiserum for one to five minutes is sufficient.

The fact that we can make the normal, non-sensitized uterus contract with antigen-antibody mixtures, which contain free antibodies in solution, cannot be brought into harmony with the conceptions which seemed safely established and required no modification by new hypothesis. This is also true for the theories of Dragstedt and his collaborators, when they state that antigen-antibody mixtures will release histamine from the blood cells when added to normal rabbit's blood. It is not necessary to go into further detail. The experimental analysis of anaphylaxis has failed to solve, or at the best has only insufficiently solved, a series of fundamental problems. It has actually brought up new questions which require answer. The theories derived from the studies of different species of animals reveal the lack of homogeneity of the conception of anaphylaxis. It is for this reason that we should not regard allergy in human beings as a simple, special type of anaphylaxis as far as its pathogenicity is concerned.

For studies in anaphylaxis, experimental reasons require the use of guinea pigs, since in this test animal we see anaphylaxis in a form in which the lethal bronchospastic shock is an easily observed and apparent phenomenon. One may be willing to view this form of reaction as a model of the asthmatic attack in man (Kallós and Kallós-Deffner<sup>25</sup>), but Walzer<sup>70</sup>, however, denies that the smooth muscle of a bronchial tree is the seat of the immunological reaction of the allergic bronchial asthma. And Rackemann<sup>53</sup>, who reported on a considerable number of deaths occurring in asthmatic individuals, states that in these patients death occurs by choking and not in consequence of a bronchial spasm. He observed a peculiar change in the bronchial secretions which were transformed into extraordinarily viscous mucus, completely blocking the lumina of the smaller bronchi as mucous plugs.

Research in anaphylaxis, it seems, has only partially fulfilled our desire for understanding and, giving us no definite answers, has at best only led us to expect one. This attitude has changed greatly since the first promising communications of Richet in 1902, and has developed slowly

over a period of four decades. Since it is not the answer, the interest in anaphylaxis, intensive at the beginning of the century, has somewhat abated.

On the other hand, the differentiation of the conceptions of allergic phenomena, seen in human beings, gives momentum to studies in medicine developed first as to the morphology of the pathological picture, and secondly as to the immunological findings and their interpretations.

I would like to make clear my point of view regarding the immunological criteria of allergy. Our discussion can begin with serum sickness, since it was in this condition that, for the first time, the question regarding the nature of the antibody arose. Although serum sickness does not correspond to the typical model of the two-phasic experiments which postulate the previous action of an antigen, von Pirquet and Schick<sup>52</sup> were in no doubt that an antigen-antibody was present. The proof in the existence of such an antibody as the cause of serum sickness was later given by Voss<sup>68,69</sup>, whose results were confirmed by Karelitz<sup>26,27,28</sup> and his collaborators.

If, in man, horse serum is injected subcutaneously and eight hours later, or perhaps several days later, the serum of a convalescent serum sickness patient is injected intravenously, there will develop, within a very short period of time, a local reaction at the site of the skin injection. If there has been an interval of four days between the two injections, the patient develops a generalized rash, which seems to originate from the point of application of the horse serum, and appears in its strongest manifestation at the site of the subcutaneous injections. This, in all its details, is an effect similar to that observed by Opie and Furth<sup>49</sup> when their rabbits were injected first with horse serum subcutaneously and four hours later with anti-horse serum given intravenously, producing by this method both local anaphylaxis and lethal shock. Insofar as I am informed, there is no doubt that this is an inverse type of passive anaphylaxis. In other words, a passive anaphylactic experiment with change in the succession of the reaction components is easily accomplished with equally positive results in guinea pigs (Zinsser and Enders<sup>72</sup>). With human serum sickness actively or passively induced, one is reluctant to acknowledge such explanations since the anaphylactic antibody is allegedly a precipitin, whereas the antibody causing serum sickness is a specific immune body not easily or simply identified with the reagins of allergy. I<sup>14,15</sup> personally held the opinion many years ago that the anaphylactic antibody was nothing else except a precipitin, and a number of authors, especially Weil, Osborne, Wells, and others agreed with me. Today I must confess that this would hold true only if we knew that the antigen-antibody reaction, which is the basis of the anaphylactic phenomenon, occurred in the animal organism with the formation of a precipitate and that the formation of this precipitate represents a primary pathogenic factor. But we do not know

this, and, on the contrary, according to the investigations of Kabat and Landow, it is not even probable. From the experiments by Tyler<sup>66,67</sup> with photo-oxidized antisera, one may deduce with the author that it is not the reaction of the antibody with the antigen which is important, but that the precipitation itself is essential and that the results could be caused by denaturation and should be controlled by observing the behavior of precipitins freed from lipoids (Hartley<sup>70</sup>). Furthermore, the flocculation termed "precipitation" is also caused by antitoxic sera and by solutions of toxins. Passive anaphylactic experiments cannot be reproduced with these components.

I do not think it of fundamental importance whether the serum of a patient suffering from serum sickness flocculates with horse serum or not<sup>9</sup>; it is essential only that an antibody be present which, in inverse-passive transfer experiments in man, functions in exactly the same way as does the anaphylactic antibody in the analogous experiment in the rabbit.

The differences between the various antibodies of orthodox serology are also, at least partly, smoothed out by the changes in our conceptions of the nature and origin of these substances. We have little doubt that all antibodies, as they are present in the blood stream, are immune-globulins, that is, serum-globulins modified by the antigen and electrophoretically falling into the pattern of gamma-globulins. This is also true according to Newell, Sterling, and their collaborators<sup>48</sup> for the reagins of pollinosis. Schönheimer, Treffers, Heidelberger, and their collaborators<sup>56,59,60</sup> were able to demonstrate with the use of tagged amino-acids containing isotope N.15 that animals in the stage of antibody production built up their antibodies, that is, their immune-globulins, from the amino-acids in their food in the same way they build up all the proteins of the organisms and that these are decomposed in the usual way. In one special case, corroborated by experiment<sup>61,62</sup>, it was estimated that the life duration of one antibody molecule circulating in the blood of the rabbit was four weeks.

In the case of the guinea pig, however, if it is sensitized with 0.01-0.001 c.c. of horse serum subcutaneously, it will, however, remain anaphylactic, not for weeks, but for more than one year, and in 1929, I concluded from this<sup>13</sup> that the production of the antibody may become independent of the stimulus by the antigen, that is, it may become autonomous. On the basis of experiments with isotope N.15 or heavy nitrogen, we may formulate that the synthesis of modified globulins, once it has started, may persist in such a way that the antibody destruction is compensated for by new antibody formation.

It is, therefore, comprehensible that the sensitization against certain foods or chemicals may remain effective for years or decades, although new contacts with the sensitizing substances are excluded. However, this behavior is not only true of anaphylaxis and of allergy; the antibodies

against measles, yellow fever, and leptospirosis, persist in the blood throughout life, not because their formation is stirred up over and over again by latent infection, but because the effect of the antigen stimulus survives the original stimulus so lastingly. Naturally enough, passively introduced antibodies are not regenerated but are destroyed. It is, therefore, the rule that immune conditions, which have been induced passively, disappear within a short period of time.

The fact that free antibodies, or globulins, which may have been synthesized in consequence of the antigen stimulus in other ways, are serum-globulins does not exclude the fact, that, although formed as a reaction of one and the same antigen, they may show differences in behavior. We must visualize the synthesis of the immune-globulin as a process reaction within the cell, variable within the boundaries of its specificity, the formation of which can be discontinued prematurely by the expulsion of the product into the blood stream. In this way, so to speak, immature antibodies may originate. The existence of such incomplete antibodies is not only comprehensible from the physiological point of view, but also their existence may be considered highly probable, as shown by the investigations of Heidelberger and Kendall<sup>22,23</sup>, Haurovitz<sup>20,21</sup> and his collaborators, Pappenheimer<sup>50</sup> and others. In view of the problems here under discussion, the fact is especially of interest that one and the same antigen may produce antibodies which give the precipitin reaction, *in vitro*, as well as others which form only a loose reversible union with the antigen and do not cause flocculation. These are merely carried along when precipitins of the first type are present and are also reacting.

In order to explain the results found in treating patients with hay fever by injections of pollen antigens, Cooke<sup>10,11</sup> assumed that in addition to the sensitizing reagin a second neutralizing antibody was formed. It was, of course, Loveless<sup>40,41,43,44</sup> who studied, in detail, the properties and therapeutic significance of this type of antibody.

This duplicity of antigen effect as seen with pollen extracts is quite compatible with the newer conceptions of the nature and origin of the antibodies. We need not return to the rigid conception of fixed type of antibodies.

Of course, it is impossible to maintain, for the present, that reagins are incomplete or imperfect antibodies. There are, however, certain similarities which make investigations in this direction hopeful, especially when we note that the reagins form easily reversible compounds and that it is because of this property that they are unable to neutralize the effect of the antigen upon the sensitized skin (Levine and Coca<sup>30</sup>). It may be that the amount of antigen and the site and method of contact all determine that, in the natural acquired sensitivity due to pollen affecting mucous membranes, only reagins are formed, but following injections of pollen extract, neutralizing antibodies occur. In this regard must

be considered the experiments of Cohen and Mosko<sup>9</sup> who state that guinea pigs sensitized intracardially with ovalbumin will consistently die in anaphylactic shock following a minimal shock dose, although very little precipitin can be shown in the circulating blood. Following intraperitoneal sensitization, precipitins are formed in a high titer, and the anaphylactic reactivities are relatively weaker and soon disappear.

When the skin of a normal individual is sensitized passively with a serum containing reagins, the site remains sensitive to antigen introduction over a period of several days or weeks. Since the local change in reactivity remains confined to the prepared site, it is assumed that the reagins are bound or anchored to the tissues of the skin. This bondage, however, is as little comprehensible as is the statement that other antibodies, that is, precipitins, cannot be bound.

If all antibodies are considered to be immune-globulins and the specific affinity to the antigen seems to make them differ from the normal globulins, this cannot be the cause of their anchorage to tissues which do not contain the antigen. Their greater persistence at the site of deposition, it seems, can be due only to their protein character, that is, they are acting as normal proteins should behave at this point, but also as immune-globulins. And this is indeed the case.

If one injects a human subject subcutaneously with horse serum and then after an interval of eight hours to several days injects the serum of a re-convalescent patient, a reaction will be seen only in the area of deposition of the horse serum, or at least the reaction, when it occurs, will be intensive at this site.

We have, in this phenomenon, an example of the valuable results to be gained by the close bond which at present exists between the problems of protein metabolism and antibody research. The complete utilization of this relationship, however, would only be possible if we were able to answer satisfactorily the genetic relationship between an antigen and its corresponding immune-globulin and were not forced to rely rather upon hypotheses, such as those brought forward by Breinl and Haurowitz<sup>3</sup>, Haurowitz<sup>20,21</sup>, Macheboeuf<sup>45</sup>, Alexander<sup>2</sup>, Mudd<sup>47</sup> and Pauling.<sup>51</sup> These hypotheses may appeal to us as far as their form and deductions are concerned, but they are, biologically, not fruitful, since they do not give us the answer as to how a reagin and a precipitin differ. This is the chief reason for the purely descriptive character of modern research in immunology, which is a purely phenomenologically differentiation of agglutinins, precipitins, lysins, antitoxins, or as le Dantec expressed himself sarcastically at one time, of "phenomenins."

It is, however, possible to extend the scope of our knowledge by the help of the experimental approach as shown by the work of Landsteiner<sup>32</sup>, working with the serological and allergic reactions of simple chemical compounds. Landsteiner<sup>35,38</sup> showed that substances like acyl chloride or picryl chloride when injected intracutaneously into the guinea pig pro-

duced a condition which in human beings might be termed contact dermatitis. But, at the same time, the animals became sensitive anaphylactically, so that they reacted to an intravenous injection of acyl or picryl protein combinations with typical anaphylactic shock. Later, Landsteiner and Chase<sup>37</sup> were able to make guinea pigs anaphylactically sensitive by intraperitoneal preparation with chemo-specific complex antigens derived from picryl chloride or 2,4-dinitrofluorbenzol, and were able as well to produce typical contact dermatitis. This occurred, however, only, if during the sensitization period, certain nonspecific factors were present.

Landsteiner<sup>33</sup> himself states that in view of these results there is no justification for defining an antigen as differing from an allergen and that it is permissible to name substances such as picryl chloride or dinitrofluorbenzol antigens because of the ease with which they lead to the production of anaphylactic antibodies.

There is another reason why we may share this point of view. Using the serum of guinea pigs sensitized by these simple substances, one may not only produce the passive anaphylactic experiment, but also sensitize the skin of a normal guinea pig by the Prausnitz-Kuestner technique.<sup>32</sup> This represents a further functional approximation of our concepts.

If the antibodies which sensitize the skin are identical with those concerned in anaphylaxis, we are not yet certain; but we may be sure that, although they differ in one or another manner, they stem from one single antigen, or, at least in the manifestation of their effects by means of a coupling of a homologous protein, that they both originate from a single immunological determinant of simple structure.

Furthermore, the occurrence of serum sickness and also pollenosis in animals under natural conditions is further confirmed by Landsteiner's studies, since we can produce drug allergy experimentally in animals and, therefore, cannot maintain the principle of the separation of allergy, as seen in human beings, from anaphylaxis, the only type of reaction seen in the lower animals. The sovereign position of "clinical allergy" is not endangered by this concept, since because of it we are able to observe the sick individual and recognize an allergic reaction as such, despite the external appearance of multiformity.

That our sources of knowledge are by no means exhausted may be seen in the works of Coca<sup>6,7</sup> on familial non-reaginic allergy, or as it was baptized with philological assistance "idioblapsie." Although through the courtesy of Dr. Coca I know of his publications, I am unable to assume any definite attitude toward this newly described form of allergic reactivity. Here the clinical re-examination of his data must have the last word.

According to the data of Coca, "idioblapsie" cannot be transmitted with the serum of the affected individual to normal individuals, or, to

put it more correctly, the passive transfer experiment by the Prausnitz-Kuestner technique is negative.

At this point, I would like to remark that all techniques of this type are primarily for the purpose of proving present, in the serum, an antibody or reagin. This is to be a substance which reacts with the antigen. We are not searching for an antibody as such, but for a specific antibody which has the property of reacting with its antigen to produce the pathological symptoms from which the donor of the serum suffers when he is affected by the antigen. We are searching for an antibody which causes hypersensitivity, or in the language of serology, for a "sensibilisin." Whether there exist, at all, antibodies which always cause this effect is very doubtful. According to present conceptions, the antigen-antibody reaction becomes pathogenic only when it occurs under very particular circumstances, under very definite but incompletely known conditions. If our understanding is correct then the experiment of transmitting an allergic reactivity may have a negative result, not because the antibody is lacking in the examined serum, but because we were unable to reproduce in the recipient just that complex of conditions necessary to produce the desired result. It may also be that the recipient is for some other reason unsuitable. Negative results, therefore, can only be used with reservations. We should remember that the Prausnitz-Kuestner experiment was, in its time, a sensational surprise, and similar surprises have since recurred several times.

For instance, in contradiction to our earlier knowledge, transfer of sensitivity from allergic humans to normal animals, as to the monkey and the guinea pig, have been made several times with certainty and unqualified success (Grove<sup>18</sup>, Caulfield<sup>4,5</sup>, Ratner<sup>55</sup>, Strauss<sup>63</sup>, Walzer<sup>77</sup>). Allergy of the type produced by simple chemical compounds was considered untransferrable. Landsteiner and Chase<sup>34</sup>, however, were able to transfer such sensitivities from the serum of highly sensitized guinea pigs to those of normal animals of the same species.

Kern<sup>29</sup> reported that he had demonstrated a chemo-specific reagin for phthallic acid anhydride in the serum of a patient with asthma and rhinitis, the symptoms of which were produced by this substance.

It was also considered that the antibody, although not demonstrable in the serum, may still be present in the body of the allergic individual, a fact which has been demonstrated beyond all doubt, in the anaphylactic guinea pig. One assumes in these cases that the antibody is bound to the cells and the tissues. A communication of Landsteiner and Chase<sup>34</sup> may be interpreted in this sense, since the experimentally produced sensitivity of the guinea pig against simple chemical compounds is transmissible with exudate cells. The proofs of the existence of antibodies housed within the cells are seen in the findings of the sensitivities of fibroblasts taken from tuberculous animals and grown in tissue cultures and found sensitive to tuberculin. This sensitivity has been maintained through

several passages in culture corresponding, of course, to several cell generations (Moen and Swift).<sup>46</sup>

Under such circumstances, it seems to me to be permissible, when the demonstration of an antibody is not possible or not constantly possible, to take refuge in the consideration that the phenomena observed in both men and animals cannot be explained in any other way than by the supposition of a pathogenic antigen-antibody reaction.<sup>36</sup> This paper outlines the actual state of the field of allergic phenomena as objectively as I can describe it. If one is bound, however, by his own work, objectivity has, I believe, certain limitations. In whatever way the definite solution of this problem is discovered, I shall be happy to live to see it defined, and I hope that the scientists in this country have a share in the achievement of this goal, a share commensurable with their merits.

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## BOTANICAL SURVEY OF SOUTHERN CALIFORNIA

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TWENTY years ago a botanical survey of allergenic plants in Southern California<sup>6</sup> was published in the *Bulletin of the Southern California Academy of Science*. More recently a survey of the San Diego region<sup>8</sup> was published in the ANNALS OF ALLERGY. Other publications<sup>2,5,7,8</sup> have appeared, dealing with various phases of this problem. Seven years of constant observation have convinced us that intelligent management of the allergic patient requires a more complete, and, at the same time, simplified statement of Southern California's pollen problem: completeness, so that the allergist may have, in one paper, access to all the facts, and simplicity so that the allergic-minded physician may have a guide for testing and treating many of the patients who do not need the more detailed studies of an allergist. It is no secret that Bermuda grass and ragweed account for a large number of cases of pollenosis in this region. It is equally true that many cases of what is apparently pure Bermuda grass hay fever will do better if they are given the benefit of more complete testing and antigen prescription as done by a competent allergist. There are, however, many hay fever and asthma sufferers who would be benefited by pollen treatment but fail to come to the allergist. This paper is an invitation to the interested physician to study his pollen-sensitive patients intelligently if he cannot send them to an allergist.

Most easterners and many Californians are under the impression that California pollens are of little importance. If one looks at the Durham<sup>1</sup> spot maps, Los Angeles looks like a haven for the ragweed sufferer, and many easterners who have had severe hay fever, and even asthma, have come to this area with complete alleviation of symptoms. Some of these people stay well; others will, after two or three years, develop symptoms again. Others come here from east of the Rocky Mountains, never having had hay fever even in that hotbed of ragweed, and develop, within months or years, severe allergic manifestations. These symptoms are frequently proved to be incited by pollen. The Los Angeles air does not ever contain great amounts of ragweed pollen. The maximum count we have ever made of downtown Pasadena air showed 20 grains per square centimeter in twenty-four hours by the gravity slide method. We have, however, made counts in a residential area only six miles from the center which ran up to 75 grains for the same slide area in twenty-four hours. This would compare in quantity with Boston, for example, where ragweed is a well recognized entity. Another factor of importance in connection with our variety of ragweed (*Ambrosia psilostachya*) is that it is a perennial, with a root system which may be 5 feet deep. Once established in a heavy

# BOTANICAL SURVEY—SMALL AND SMALL

soil, which it likes, it is practically impossible to eradicate, except by planting it out with several years of grain crops. Pulling it up does little more than discourage it for a while. It is particularly prevalent in vacant

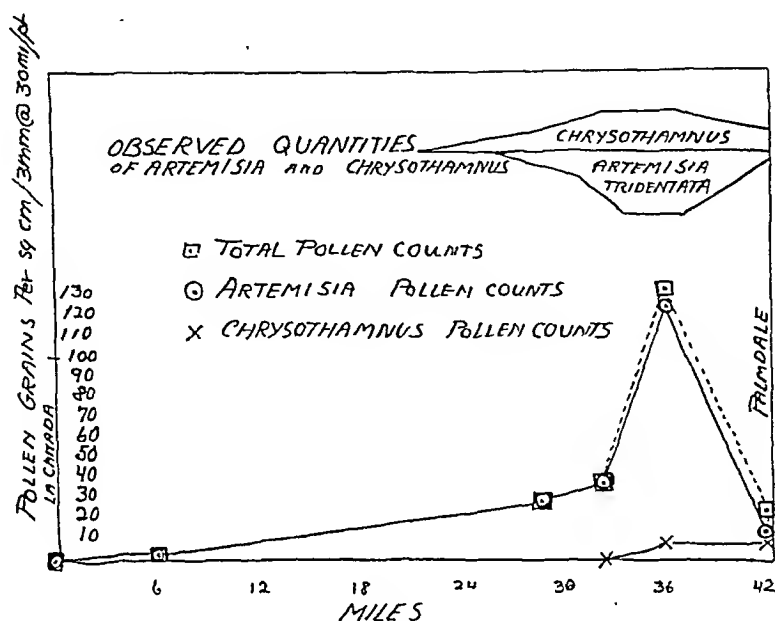


CHART I

lots in partially built-up residential areas and is increasing in quantity. Last but not least there are several close relatives of ragweed which will be discussed in more detail later in this paper.

For many years it has been stated that the pollen of a plant must have the following characteristics to be a hay fever factor: (1) wind blown, (2) of high toxicity, (3) present in sufficient quantity. I think very few allergists will argue the question of toxicity of chrysanthemum or golden rod in many persons. Neither will a competent allergist recommend banks of these flowers in the patient's room. The golden piles of pollen on the table are clear evidence of the large quantities produced and dropped by these plants. A recent trip by automobile gave a pretty clear demonstration of two facts: (1) quantity of plant as determined by observation is roughly proportioned to the actual quantity of pollen in the air during its flowering season; (2) the total quantity of pollen caught on the slide was greater from the wind blown plant (*Artemisia tridentata*), but was also present in appreciable quantity from a plant which would ordinarily be classified as an insect pollinated plant (*Chrysanthamnus*). This survey was made by driving from Pasadena across the San Gabriel mountains to the Mojave Desert (black line on map). There is a very large quantity of sagebrush (*Artemisia tridentata*) just over the ridge and near the floor of the desert. In a wider area in this same location, there is a very

large quantity of *chrysanthamnus*. There are no other compositae in any appreciable quantity in this locality. Glycerine jelly slides were exposed for three minutes outside of the car which was driven at 30 miles an hour. The curves on the accompanying chart show the pollen counts per square centimeter at various intervals along the road.

From previous experience with this method in comparison with twenty-four hour slides, it has been found that the counts are roughly comparable. The inference may therefore be drawn that there was half as much *Chrysanthamnus* pollen in the air at this location on this day as there is ragweed at the height of the season in Pasadena, and this plant is as much insect-pollinated as is eastern goldenrod. The other point of importance is that where one observes large quantities of a known hay fever producer, there one will find large quantities of pollen during the season of pollination. We have checked this phenomenon so carefully that we feel our method of observing hay fever plants quantitatively is our most accurate guide.

In the paper by Dr. Harsh<sup>3</sup>, he gave an ingenious method of calculating this quantitative factor. Briefly, his method was based on the quantity of pollen he obtained from cut flowering stems which were placed in water and allowed to shed their pollen over paper. In our experience this method, although highly satisfactory for collecting pollen, is likely to give an erroneous impression of quantity of pollen given off under natural conditions. We have had many experiences in collecting branches of pollinating weeds, only to find that removal from the root resulted in their failure to shed appreciable amounts of pollen, whereas another branch of the same plant, which appeared to be in the same stage of flowering, would continue to pollinate for days when not severed from the growing plant. This factor is quite variable from species to species.

The problem of specificity has been a hot point for discussion among allergists for years, and the number of papers pro and con is appalling. In general, those who have had good ground work in immunology believe firmly in the necessity of being highly specific in selecting their pollens for treatment. Among the most convincing arguments for this side of the controversy was that contained in Phillips' paper<sup>4</sup> on the introduction of the sugar beet seed industry in and around Phoenix, Arizona. In this paper he showed, with great clarity, that in spite of treatment with related *Chenopodiaceae*, sugar beet pollen was required in his antigens for certain patients. In spite of this, and a few other critical studies, many allergists—particularly those east of the Rocky Mountains—seem to get good results with timothy in their grass hay fever cases. I think, however, very few southern allergists would attempt to treat their Bermuda grass cases with timothy.

We have been impressed for many years with the similarity of skin reactions among closely related plants. For example, the vast majority

of ragweed sensitive patients show positive reactions to all of the ambrosias and franserias, particularly if great care is used in keeping the extracts used for testing of uniform strength and reasonably fresh. There is, however, an occasional patient in whom an ophthalmic test with *Ambrosia psilostachya* may be of different degree from the test with *Franseria acanthicarpa*, and the same situation occurs occasionally with the skin test. With these facts in mind, it has not seemed necessary to do the enormous number of pollen tests which have been done by some of the men in the field, but in making the antigen we are extremely careful in our selections. For example, a patient who has symptoms in the fall, lives in the Pasadena area, is found sensitive to ragweed and *Franseria*, is treated specifically with *Ambrosia psilostachya* and *Franseria acanthicarpa*. If, however, he happens to spend his winters in Palm Springs, and has difficulty in February and March there, *Franseria dumosa* and probably *Hymenoclea salsola* are added. Sensitivities to these pollens would, of course, be determined in his case. These two latter pollens would be disregarded in the ragweed-sensitive person who lives near the beach and has trouble in April or May. In this case, *Franseria bipinnatifida* would be added.

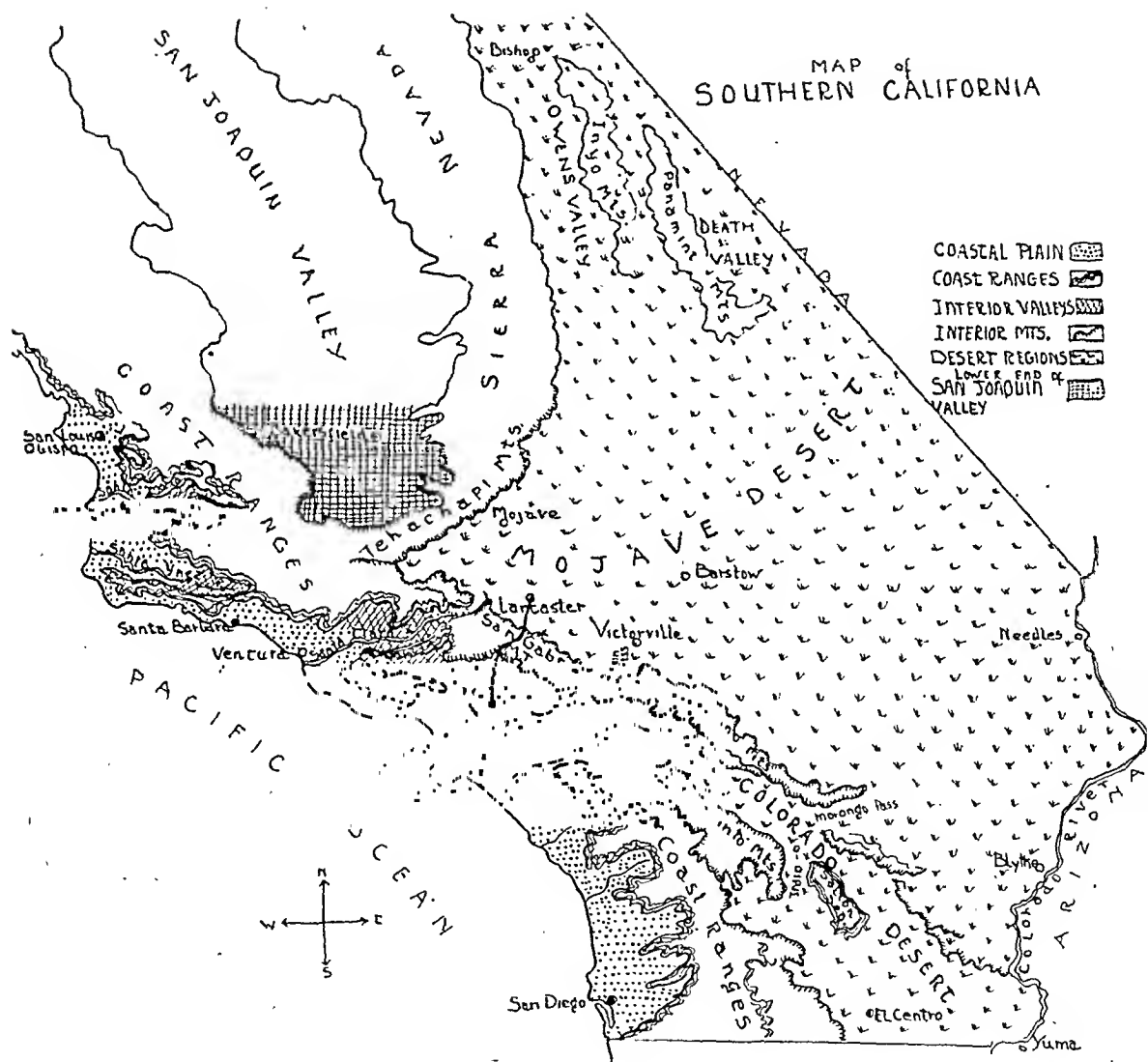
The traveling salesman may need very careful study—history being of vital importance, according to regions visited. The map will aid in understanding these regions better.

Although the botany of southern California is a very complex affair, we have attempted to simplify and clarify the problem: (1) by listing on a geographical basis, and (2) by using three kinds of type in the lists. The capital-lettered listings are, in our opinion, the most wide-spread and most frequent offenders. With careful history and testing one will find some patients who will have clinical symptoms from certain of the black type pollens. The light type attempts to list most of the other possible offenders. A supplementary list is added at the end of the regional lists. These are plants that should be known and could be considered in certain cases, such as in farmers, inhabitants of brushy hills, or children who play in fields. Included are: (a) anemophilous plants (wind-pollinated) of low antigenicity; (b) entomophilous plants (insect-pollinated) occurring in large quantities, forming the main covering in certain areas, some producing great amounts of pollen after the rains are over; (c) occasional anemophilous plants of known antigenicity (ornamental or native).

An occasional person may have some ornamental tree or shrub in his yard which is his primary cause of trouble. A home visit will at times solve the problem. Large flower gardens of plants containing highly toxic pollen may at times be the causative factor.

We have considered southern California to be that portion of the state lying south of a line between Morro Bay and Kingston, Nevada, latitude 35. Southern California may be divided into the following

# BOTANICAL SURVEY—SMALL AND SMALL



## BOTANICAL SURVEY—SMALL AND SMALL

geographical regions: (1) *the Coast Ranges*, (2) *the Coastal Plain*, (3) *the Interior Ranges*, (4) *Interior Valleys*, (5) *the Desert Regions*—of which this survey covers two definite regions: (a) the Colorado Desert, (b) the Mojave Desert, including Owens Valley, (6) *Southern End of the San Joaquin Valley*.

A brief description of each region follows.

1. *Coast Ranges of Southern California*.—These are divided into two large masses by the Los Angeles Basin where three rivers enter the sea. The northern section is a broad mass of broken chains running parallel to the coast and at various angles to it. Included in this mass are the southern end of the Santa Lucia Mountains, the mountains of Santa Barbara and Ventura counties, the Santa Susanna Mountains and the Santa Monica Mountains. They range up to about 4,000 feet in altitude. Most of the vegetation belongs to the Upper Sonoran life zone and consists in great part of a dense covering of shrubbery known as the hard chaparral. The most common genera in this pigmy forest, or chaparral, are *Ceanothus*, *Adendostoma*, *Quercus*, *Cercocarpus*, *Arctostaphylos*, *Rhus* and *Rhamnus*. Most of these plants produce heavy bloom in the spring, although only *Quercus* and *Cercocarpus* are definitely wind-pollinated. In the more northerly sections *Castanopsis sempervirens* is a common wind-pollinated shrub. The pollen season of the chaparral extends from January, when *Ceanothus cuneatus* and *Ceanothus crassifolius* begin, until the middle of June when *Adendostoma fasciculatum* finishes. The chaparral then becomes very dry and goes into a dormant state. Oaks, sycamores, alders and cottonwoods grow in the canyons of these ranges and California black walnut (*Juglans californica*) is very common on the eastern slopes. The western slopes of the hills up to about 1,500 feet are characteristically covered with grasses, *Avena fatua* being the most common, with vast amounts of *Artemisia californica* and *Salvia* interspersed. *Artemisia californica* increases upwards from the coastal plain, meeting and blending with the chaparral belt, finally being ruled out by the dense growth of shrubs. This *artemisia* appears wherever there is a clearing of chaparral and again in large quantities on the lower eastern slopes, with grasses. Between the ranges of hills and mountains are pleasant grass covered valleys. Rank summer weeds grow along the streambeds, especially *Artemisia vulgaris*. The grasses of this region are spring pollinating.

South of Los Angeles the coast ranges begin with the Santa Ana Mountains and sweep out toward the sea north of San Juan Capistrano, continuing near the sea to San Diego, though indented by numerous valleys. These mountains include the Laguna Mountains, the Cuyamaca Mountains and all the mountains of San Diego County except the Santa Rosas and the mountains bounding the desert. These innumerable rugged chains compose a thick mountain mass, somewhat higher in elevation

than the northern coast ranges. It becomes ever more arid to the east, ending in true desert mountains.

The chaparral belt of the southern coast ranges is similar to that of the northern section, although somewhat less luxurious in growth and containing more *Adenostoma*. The valleys and seaward slopes are grassy and there are great quantities of *Artemisia californica* all through the ranges and valleys, the chaparral being less dense. On some of the higher ridges there is timber of oak and evergreen trees, while sycamore, oaks and cottonwoods thrive in all the canyons.

2. *The Coastal Plain*.—Three practically parallel belts characterize this section.

(a) The beaches have a sparse zerophytic flora. Here *Franseria bipinnatifida*, forming mats upon the dunes, is of allergenic importance.

(b) Between the beach and the plain, there is a band of halophytes, plants adapted to excess mineral soil content (salt, alkali). The many species of *Atriplex* are characteristic and abundant members of this band. Where the hills recede at drainage basins, these halophytic plants spread out into marshes and wastelands, sometimes stretching for miles inland. For example, *Atriplex breweri* follows the Santa Clara River inland as far as Castaic and beyond, over forty miles. The southwesterly section of the Los Angeles Basin, where the Los Angeles River and the San Gabriel River approach the sea, is a broad area over ten miles square of marshes and waste flats, covered with various members of the Chenopodiaceae. This land, however, is being gradually converted into agricultural fields and industrial or residential sections, thereby changing the atmospheric pollen content.

(c) The plain itself is a fertile band of soil originally grass-covered, that stretches along the coast to the base of the hills. At times narrow, it widens into large areas where the hills recede. These latter areas are cultivated, yielding many rich crops, and sustain large populations. The coastal towns are situated on this plain, hence we find in this section grass lands and cultivated lands with crops and ornamental plants.

3. *Interior Ranges*.—These mountains are: (a) the Tehachapi Mountains, which may be visualized as a continuation of the Sierra Nevada, swinging south and west to join the coast ranges, bounding the lower end of the San Joaquin Valley on the south and the Mojave Desert on the north; (b) the San Gabriel Mountains; (c) the San Bernardino Mountains; (d) The San Jacinto Mountains which pass southward into the rugged ranges of the Santa Rosas. These interior mountains are covered for the most part, as are the coast ranges, with solid hard chaparral but in their higher altitudes, from about 5,000 feet, the flora of the Transition Zone flourishes, with timber of pine and deciduous oak.

The important allergenic plant *Artemisia tridentata* or Mountain Sage

Brush grows in quantities on the northern and eastern slopes of the San Gabriel and San Bernardino Mountains, forming a band between the desert growth and the chaparral, growing at increasing altitudes going south, and filling large valleys and plateaus in the San Bernardinos. It also grows in abundance on the eastern slopes of the Santa Rosa Mountains. The dates of pollination of this plant vary strictly according to altitude. It starts to bloom the 15th of August at 7,000 feet, and not until the last of October or even later at 2,000 feet.

There are a few shrubs in the chaparral of allergenic importance, not necessarily typically wind-pollinated plants, but because of the great masses of flower and the extreme dryness of the atmosphere this pollen at times becomes a factor. The fact that both children and adults spend vacation time in the mountains gives these plants importance.

On the foothills we find again, as in the coast ranges, quantities of *Artemisia californica*. The pollinating habits of this plant are interesting and worth noting. Along the coast where the air contains more moisture and the plants are washed by summer fogs, the coastal sage has a regular pollination season, July and August. On the hills surrounding the interior valleys and on the foothills of the inland ranges its habits of pollination are variable, due to increased aridity and dryness of the air. It is dormant in the summer, withered in appearance. It begins to form buds, however, in late September. After the first good autumn rain these grow, and almost exactly eighteen days after the rain these buds burst into bloom, the pollen being all dissipated in about one week. Some years when there are light rains in the fall some bushes, apparently those receiving enough moisture, will bloom while others will await heavier rains. In 1939, the majority of these plants pollinated for two weeks in the middle of January after a dry fall and heavy rains the first of January. This is an example of adaptation to semi-desert conditions.

4. *Interior Valleys*.—These valleys are: (a) the Los Angeles Basin, composed of the San Gabriel Valley and the San Fernando Valley; (b) the San Bernardino Valley crossed by the Santa Ana River, and the Santa Ana River Valley in Orange County; (c) the Santa Clara River Valley in Ventura and Los Angeles Counties; (d) the Santa Inez River Valley, the Santa Ana River Valley and other smaller valleys drained by rivers rising in the coast and interior ranges. These valleys stretch inland along rivers or lie between the coast and inland ranges. They are all rich, irrigated and cultivated to concentrated groves and field crops. Here is the best home for *Ambrosia psilostachya* and *Sorghum halepense*, both of which grow abundantly with other rank weeds in ditches, stream beds and around irrigated and fallow fields. The beds of all these rivers are wondrous weed gardens, all the summer and fall wind-pollinated weeds growing together in luxurious profusion. In these same river beds cottonwoods and sycamores rain pollen in the spring.

5. *Desert Regions*.—This vast region comprises all of California, lying east and south of the Sierra Nevada, east of the Tehachapi, north of the San Gabriel, northeast and south of the San Bernardino, east and south of the San Jacinto and east of the Santa Rosa Mountains and the mountains of San Diego county, and stretching to the Colorado River. Although the two deserts fuse and authorities differ as to boundaries, we consider in this paper the boundary between the Mojave and the Colorado Deserts to be approximately a line extending from Morongo Pass eastward to Riverside Mountain on the Colorado River.

(a) The *Colorado Desert* lies at a low altitude, mainly from 100 feet below to 1,500 feet above sea level. Palm Springs and other winter resorts are situated in the Coachella Valley in the northeastern end of the desert. *Hymenoclea salsola* is plentiful in this region, and it puts out prodigious amounts of pollen which looks similar and is antigenically closely related to the ragweeds. It blooms in February and March. *Franseria dumosa* is also abundant here and begins to pollinate in March, so that there is a long season for the *Ambrosiac* (ragweed tribe). *Dicoria*, another relative of ragweed, is also here in quantity. Farther south, in the Imperial Valley, there is a large permanent population. Irrigated fields account for rank growths of weeds, particularly *Atriplex*, and grasses. Bermuda grass is abundant and blooms practically the year round. Species of *Chenopodiaceae* abound from north of the Salton Sea to the Mexican border, there being an impenetrable jungle of *Atriplex lentiformis* spreading for miles around the shores of the Salton Sea, and acres covered by solid masses of other species.

(b) The *Mojave Desert* lies at a higher level than the Colorado Desert, the altitude ranging from 2,000 to 5,000 feet above sea level. The rainfall is usually somewhat greater, the winters colder. Here again we find *Artemisia tridentata*. Although this plant occurs on the desert slopes of the San Jacinto and the Santa Rosa Mountains, it is much more extensive in range and quantity in the Mojave Desert, occupying large tracts on the eastern slopes of the Sierra Nevada Mountains and the Tehachapi Mountains, on the western mountain boundaries, and in the northern part of this desert, passing on to cover large parts of Owens Valley and Mono County. At its northern end the Mojave gradually passes into the Owens Valley, of which Bishop is the principal town. This long valley is bounded by the Inyo Range on the east and the Sierra Nevada on the west. It was originally a natural sink, the old borders of the lake and the surrounding land being strongly alkaline, hence we find the *Chenopodiaceae*, and other halophytic plants of the Lower Sonoran life zone. This area is included in this survey because many Southern California people travel through here, spring, summer and fall, on their way to the Sierra Nevada, Lake Tahoe and Nevada.

6. *Southern End of the San Joaquin Valley*.—This section is also a sink without drainage and much of the soil is alkaline. Again we find that the

## BOTANICAL SURVEY—SMALL AND SMALL

natural vegetation of the floor of the basin belongs to the Lower Sonoran life zone, with Chenopodiaceae and other plants conditioned to alkalinity growing in profusion. There are now large areas under irrigation stretching out from Bakersfield, and in these sections we find rank weeds and grasses. The hills surrounding on all sides are natural range lands, characteristically covered with indigenous grasses, and widely spaced deciduous oaks (*Quercus lobata*).

### DISCUSSION

It can be seen from the map that a person living in Pasadena would be subjected to pollens from interior valleys and coast ranges. If, however, he travels around occasionally, as we all do, he may get into any of the other divisions. Primary consideration should be given to his close environment.

If a person lives in Beverly Hills and works in Los Angeles, he is subject to pollens of the interior valleys, coast ranges and, when the wind is from the west, pollens from the coast lowlands are likely to reach him. Two or three times yearly Los Angeles is subject to the "Santana" or desert wind. This may bring him interior range pollens and even desert varieties.

Another factor to be remembered is that there is generally no rain from April to November except in the high mountains. In spite of the fact that insects collect pollen there is still much left on leaves and stems. When the dry desert winds blow we have seen varieties of pollen which we knew had been shed weeks and months previously.

Although the lists are long and complicated we have found that routine testing for residents of the Los Angeles area may safely be limited to about thirty. Checking the list will give the key to which these are. A resident of Mojave would need even fewer tests. For the past four years we have made it a rule to check all doubtful and negative pollen reactions by either the ophthalmic or intranasal method, and have been able to turn up some reactors by this method who would otherwise have been missed.

In conclusion, we think that southern California has perhaps the greatest number and widest variety of possible hay fever producing plants to be found anywhere in the United States, but we do not have tremendous quantities of pollen contaminating the air of our cities. We do, however, have much longer seasons of the ragweeds and grasses. It is our hope that this paper will make it possible for those physicians who are interested in asthmas and hay fevers to understand the problem, test with the pollens of their area, and treat with specific pollen antigens.

The botany of a growing community like the Los Angeles area is not a static thing. In the past twenty years the building program in West Los Angeles, for example, has been enormous. Very large areas of what was then full of the halophytic plants are now almost completely covered

# BOTANICAL SURVEY—SMALL AND SMALL

by stores and residences, so much so that some of the species reported twenty years ago have almost disappeared in this area.

## Lists of Allergenic Plants Divided into Geographical Areas

### I COAST RANGES

#### WEEDS

##### Compositae

ARTEMISIA CALIFORNICA	Coast Sage Brush	September
AMBROSIA PSILOSTACHYA	Western Ragweed	July 15-Sept.
ARTEMISIA VULGARIS		
HETEROPHYLLA	California Mugwort	July-Aug.
Franseria acanthicarpa	False Ragweed	June-July
Xanthium canadense	Cocklebur	Summer
ARTEMISIA TRIDENTATA	Mountain Sage Brush	Sept.-Nov.

Artemisia tridentata is not a plant of the Coast Ranges, but rather is characteristic of higher altitudes in the Great Basin. However, it occurs in the mountains of San Diego County. Beginning at a line running through Campo, Pine Valley and Cuyamaca north, it spreads east toward the desert as far as Imperial County, appearing in great abundance in flats and valleys in these arid mountains. It also occurs in the east slopes of the Santa Rosa Mountains of Riverside and San Diego Counties.

##### Chenopodiaceae

Chenopodium album	Lamb's Quarters	May-Sept.
Chenopodium ambrosioides	Mexican Tea	Summer

##### Amaranthaceae

Amaranthus retroflexus	Pig Weed	Spring-Summer
Amaranthus graesizans	Tumble Weed	Spring-Summer

#### GRASSES

CYNODON DACTYLON	Bermuda Grass	Feb.-Nov.
Avena fatua	Wild Oats	Feb.-May
Poa annua	Annual Blue Grass	Spring-Summer
Bromus species	Brome Grasses	Mar. 15-May 15
B. mollis	Soft Chess	
B. rigidus	Ripgut Grass	
B. molliformis		
B. rubens	Red Brome	
B. carinatus	California Brome	
B. racemosus		
Elymus condensatus	Giant Rye Grass	May 20-July
Elymus glaucus	Blue Rye Grass	April 15-June
Festuca myuros	Fescue	March-April
Festuca megalura	Fescue	March-April
Hordeum murinum	Fox-tail	March-April
Poa pratensis	Kentucky Blue Grass	
	(Lawns and escapes)	
Stipa pulchra	Needlegrass	April-May
Stipa lepida	Needlegrass	April-May

#### SHRUBS AND TREES

##### A. Native Shrubs and Trees

QUERCUS AGRIFOLIA	Coast Live Oak	March-April
PLATANUS RACEMOSA	Sycamore	March-April
JUGLANS CALIFORNICA	So. Calif. Black Walnut	Feb. 15-May
Quercus dumosa	Scrub Oak	March-April
Populus fremontii	Cottonwood	March-April
Salix lasiolepis	Arroyo Willow	Feb.-March
Ceanothus spinosus	Red Heart	April-May
Ceanothus macrocarpus	Wild Lilac	April-May

The following species of Ceanothus are also common in the coast ranges: C.

## BOTANICAL SURVEY—SMALL AND SMALL

crassifolius, *C. cuneatus* (inner ranges), *C. divaricatus* (drier ranges), *C. verrucosus* (San Diego County). *Ceanothus* comprises the principal component of the chaparral. The bloom is heavy and the pollen though not strictly wind-pollinated is prolific, and continues from January 1 through May, as the different species pollinate successively.

<i>Garrya vetchii</i>	Silk tassel	March-April
<i>Garrya fremontii</i>	Silk tassel	March-April
<i>Castanopsis sempervirens</i>	Chinquapin	June-July
B. Ornamental and Crop Trees. (Planted around settlements).		
OLEA EUROPAEA	Olive	May 25-June
JUGLANS REGIA	English Walnut	April
<i>Ligustrum japonicum</i>	Privet	May
<i>Acacia</i> species		January-June
<i>Acacia floribunda</i> flowers throughout the year. For list of species see Interior Valleys list.		

### II COASTAL PLAIN

#### WEEDS

Chenopodiaceae		
ATRIPLEX LENTIFORMIS		
BREWERI	Lenscale	June-August
ATRIPLEX SPECIES:		
A. bracteosa	Bractscale	June-August
A. hastata	Spearscale	June-Sept.
A. rosea		
A. argentea-expansa	Silverscale	June-July
A. decumbens		
<i>Chenopodium album</i>	Lamb's Quarters	May-Sept.
<i>Salsola kali</i>	Russian Thistle	June-August
<i>Beta vulgaris</i>	Sugar Beet	April-June
<i>Suaeda californica</i>	Sea-blite	May-August
<i>Salicornia ambigua</i>	Samphire	June-Sept.
<i>Chenopodium ambrosioides</i>	Mexican Tea	June-Sept.

#### Compositae

ARTEMISIA CALIFORNICA	Coast Sage Brush	September
AMBROSIA PSILOSTACHYA	Western Ragweed	July 15-Sept.
ARTEMISIA VULGARIS		
HETEROPHYLLA		
<i>Franseria bipinnatifida</i>	Calif. Mugwort	July-August
<i>Franseria acanthicarpa</i>	Sand Bur	April-Sept.
<i>Artemisia dracunculus</i>	False Ragweed	July-Sept.
<i>Hymenoclea monogyra</i>		Summer
(San Diego County and Lower California only.)		

#### GRASSES

##### Graminae

CYNODON DACTYLON	Bermuda Grass	Jan.-Nov.
DISTICHLIS SPICATA	Salt Grass	Spring-Summer
SORGHUM HALEPENSIS	Johnson's Grass	Summer
(Holeus halepensis)		
LOLIUM MULTIFLORUM	Italian Rye Grass	May-June
<i>Avena fatua</i>	Wild Oats	Feb.-May
<i>Elymus triticoides</i>	Wild Rye Grass	May-July
<i>Elymus condensatus</i>	Giant Rye Grass	May-July
<i>Bromus</i> —5 species	Brome Grass	
See list under Coast Ranges		
<i>Hordeum murinum</i>	Foxtail	March-April
<i>Hordeum nodosum</i>	Mouse-tail	March-April
<i>Phalaris minor</i>	Canary Grass	April-May
<i>Phalaris paradoxa</i>	Canary Grass	April-May
<i>Phalaris canariensis</i>	Canary Grass	April-May
<i>Polypogon monspeliensis</i>	Bear Grass	April-May

#### TREES

JUGLANS REGIA	English Walnut	April
QUERCUS AGRIFOLIA	Coast Live Oak	March-April

## BOTANICAL SURVEY—SMALL AND SMALL

PLATANUS RACEMOSA	Sycamore	March-April
OLEA EUROPAEA	Olive	May 25-June
Ligustrum japonicum	Privet	May
Acacia species	Acacia	Jan.-May
Salix lasiolepis	Arroyo Willow	Feb.-March
Ulmus parvifolia	Evergreen Elm	Oct.-Nov.

### III INTERIOR RANGES

#### WEEDS

##### Compositae

ARTEMISIA CALIFORNICA	Coast Sage Brush	After all rains
ARTEMISIA TRIDENTATA	Mountain Sage Brush	Sept.-Nov.
Artemisia vulgaris heterophylla	Calif. Mugwort	July-Aug.
Chrysothamnus nauseosus	Golden Bush, Rabbit Bush	Sept.-Oct.
Artemisia vulgaris varieties	Mugwort	July-Aug.
Artemisia dracunculus		Summer

##### Other Families

Salsola kali (occasional)	Russian Thistle	April-Sept.
Plantago lanceolata (occasional)	Plaintain	Spring

#### GRASSES

##### Graminac

Bromus tectorum	Downy Cliess	Spring
Bromus rubens	Red Brome	Late Spring
Elymus condensatus	Giant Rye Grass	May-June
Elymus triticoides	Wild Rye Grass	May-June
Hordeum nodosum	Mouse-tail	June
Poa secunda	Sandberg Blue Grass	Early Summer
Agrostis lepida		Early Summer
Muhlenbergia rigens	Deer Grass	Summer
Stipa pulchra	Needlegrass	May-June
Stipa coronata	Giant Stipa	May-June

#### TREES AND SHRUBS

QUERCUS CHRYSOLEPIS	Canyon Oak	April
QUERCUS DUMOSA	Scrub Oak	April
QUERCUS KELLOGGII	Black Oak	June

This oak is prolific in the higher parts of the San Bernardino and San Jacinto Mountains, foresting large stretches. It also grows in the higher sections of the San Diego Mountains.

Quercus agrifolia	Coast Live Oak	March-April
Ceanothus cuneatus	Buck Brush	Jan.-Feb.
Ceanothus divaricatus	Deer Brush	March-April
Ceanothus greggii and other species		Spring

Plantanus racemosa	Sycamore	March-April
Populus fremontii	Cottonwood	March-April
Juglans californica	So. Calif. Black Walnut	April-May
Alnus rhombifolia	Alder	Jan.-Feb.
Salix species	Willow	Feb.-March
Castanopsis sempervirens	Chinquapin	June-July
Garrya veatchii (not abundant)	Silk tassel	March-April

The Tehachapi Mountains, being more arid, differ in some respects from the rest of the interior mountains. The weeds, grasses and chaparral are similar, with the addition of some *Atriplex canescens* and *A. lentiformis*. *Artemisia tridentata* is found in quantities in the high central valleys and on the slopes toward the desert. The spring grasses are like the grasses of the Coast Ranges, including the Brome grasses, *Avena fatua*, *Elymus condensatus*. *Elymus triticoides* fills the mountain meadows. On the ridges grow *Quercus douglasii* (Blue Oak) taking the place of *Quercus kelloggii*, while *Quercus lobata* grows in the valleys. *Quercus agrifolia*, *Q. chrysolepis* grow on the slopes. *Pinus cembroides monophylla* (One-leaf Pinon) and *Pinus sabiniana* (Digger Pine) take the place of the Yellow and Sugar Pines of the other interior mountains.

# BOTANICAL SURVEY—SMALL AND SMALL

## IV INTERIOR VALLEYS

### WEEDS

#### Compositae

AMBROSIA PSILOSTACHYA	Western Ragweed	July 15-Oct.
FRANSERIA ACANTHICARPA	Western False Ragweed	Aug.-Oct.
ARTEMISIA CALIFORNICA	Coast Sage Brush	Sept.-Jan.
ARTEMISIA VULGARIS		
heterophylla	Calif. Mugwort	July 15-Aug.
Helianthus annuus	Sun Flower	Aug.-Oct.
Artemisia dracunculus		Spring, Summ., Fall
Franseria tenuifolia	Slender False Ragweed	Summer
Chrysothamnus nauseosus	Golden Bush, Rabbit	Aug.-Sept.
varieties	Bush	Aug.-Oct.
Chrysothamnus viscidiflorus	Golden Bush	Aug.-Sept.
Xanthium canadense	Cocklebur	Spring-Summer
Xanthium spinosum	Spiny Clotbur	Spring-Summer
(Very localized, in neglected fields).		

#### Chenopodiaceae

SALSOLA KALI	Russian Thistle	April-Nov.
CHENOPODIUM ALBUM	Lamb's Quarters	Spring-Summer
Chenopodium murale	Nettle-leaf Goosefoot	Spring-Summer
Chenopodium ambrosioides	Mexican Tea	Spring-Summer

#### Amaranthaceae

Amaranthus retroflexus	Rough Pigweed	Spring-Summer
Amaranthus graesizans	Tumbleweed	Spring-Summer
Amaranthus palmeri	Careless Weed	May-July
(San Bernardino County, and west through Arizona).		

### GRASSES

#### Graminae

##### A. Spring Grasses (Mostly native and annual).

CYNODON DACTYLON	Bermuda (Perennial)	Jan.-Nov.
POA ANNUA	Annual Blue Grass	March-June
Avena fatua	Wild Oats	Feb.-April
Bromus species	Brome Grass	
B. mollis	Soft Chess	
B. rigidus	Ripgut Grass	
B. molliformis		
B. rubens	Red Brome	
B. carinatus	California Brome	
B. racemosus		
Festuca myuros	Fescue Grass	Feb.-April
Hordeum murinum	Wild Barley, Foxtail	March-April
Festuca megalura	Fescue	Feb.-April
Hordeum vulgare	Barley	March-April

##### B. Summer Grasses (Perennials, many introduced species).

CYNODON DACTYLON	Bermuda	Jan.-Nov.
SORGHUM HALEPENSIS	Johnson's Grass	Summer-Fall
Poa pratensis	Kentucky Blue Grass	May-June
Lolium perenne	Perennial Rye or Ray Grass	May-June
Lolium multiflorum	Italian Rye or Ray Grass	May-June
Daactylis glomerata	Orchard Grass	May-Sept.
Elymus triticoides	Wild Rye Grass	May-July
Elymus glaucus	Blue Rye Grass	May-July
Elymus condensatus	Giant Rye Grass	May-July
Agrostis palustris	Cocoos Bent Grass	May-July
Agrostis verticillata	Whorled Bent Grass	May-July
Echinochloa crus-galli	Barnyard Grass	July-Sept.
Setaria viridis	Bristle Grass	July-Sept.
Stipa pulchra	Purple Needle Grass	May-July

# BOTANICAL SURVEY—SMALL AND SMALL

Stipa lepida	Needle Grass	May-July
Zea mays	Indian Corn	June-Aug.
(Strictly localized)		

## SHRUBS AND TREES

A. Native species; canyons, washes, hills.		
QUERCUS AGRIFOLIA	Coast Live Oak	Mar. 15-April
QUERCUS DUMOSA	Scrub Oak	Mar. 15-April
JUGLANS CALIFORNICA	So. Calif. Black Walnut	Feb.-May
PLATANUS RACEMOSA	Sycamore	Mar.-April
POPULUS FREMONTII	Cottonwood	Mar.-April
Ceanothus species		
C. crassifolius		Spring
C. cuneatus		Jan.-Feb.
Alnus rhombifolia	Alder	Jan.-Feb.
Salix species	Willow	Feb.-March
B. Ornamental and Crop Trees.		
OLEA EUROPAEA	Olive	May 25-June
JUGLANS REGIA	English Walnut	March-April
Acacia species	Acacia	Feb.-June
A. decurrens		
A. baileyana		Jan.-Feb.
A. melanoxylon	Black Acacia (Common street tree)	
A. latifolia		
A. floribunda		
Schinus molle	Pepper Tree	Late Spr.-Summ.
Ricinus communis	Castor Bean	Early Spring
Ulmus parvifolia	Evergreen Elm	Sept.-Oct.
Rosaceae	Rose Family	May-June
A great many shrubs, native and planted, of this family, bloom all at the same time in the late spring and early summer. The following common genera are included: Rosa, Prunus, Pyracantha, Photinia, Cotoneaster.		
Ligustrum japonicum	Privet	May-June

## V DESERT REGIONS

Part 1. The Mojave Desert, including Antelope Valley and Owens Valley.

A. Open desert; indigenous species.

Compositae		
FRANSERIA DUMOSA	Burro Bush	Feb.-April
ARTEMISIA TRIDENTATA	Mountain Sage Brush	Oct.-Nov.
HYMENOCLEA SALSOLA		Feb.-April
Dicoria brandegii		Aug.-Oct.
Chrysothamnus nauseosus varieties	Rabbit Bush	Aug.-Oct.
Chenopodiaceae		
ATRIPLEX POLYCARPA	Allscale	May-June
ATRIPLEX CANESCENS	Wingscale	May-June
SALSOLA KALI	Russian Thistle	Apr.-Sept.
Grayia spinosa		May-June
Atriplex argentea expansa	Silverscale	July
Atriplex lentiformis	Lenscale	June-July
Suaeda suffrutescens		May-June
Eurotia lanata		May-June
Allenrolfea occidentalis		May-June
Sarcobatus vermiculatus		May-June
Kochia americana californica		March
Graminae. Grasses		
Distichlis spicata	Salt Grass	March-May
Bromus tectorum	Downy Chess	March-April

# BOTANICAL SURVEY—SMALL AND SMALL

Bromus rubens	Red Brome	March-April
Hilaria rigida	Galleta Grass	Late Spring
Triodia pulchella	Frost Grass	Late Spring
Panicum urvilleanum	Desert Panic Grass	Late Spring
Stipa	Needle Grass	March-April

## Other families

Ephedra nevadensis (Gnetaceae)	Ephedra	Spring
Ephedra viridis	Ephedra	Spring

## B. Irrigated sections; around farms, towns, habitations.

### WEEDS

SALSOLA KALI	Russian Thistle	April-Sept.
FRANSERIA ACANTHI-CARPA	False Western Ragweed	Aug.-Oct.
AMBROSIA PSILOSTACHYA	Western Ragweed	July-Aug.
This is not found in the southern section of Mojave Desert, nor in Antelope Valley, but it is occasional in Inyo County.		
Amaranthus graesizans	Tumble Weed	Spring-Summer

### GRASSES

Distichlis spicata	Salt Grass	March-May
Elymus triticoides	Wild Rye Grass	May-June
Lolium multiflorum (Inyo County)	Italian Rye Grass	Summer
Phleum pratense (Inyo County)	Timothy	Summer
Agrostis species	Bent	Spring-Summer
Elymus glaucus	Blue Wild Rye	May-June

### TREES

Populus fremontii	Cottonwood	March-April
Olea europaea (Few).	Olive	May-June

## Part 2. The Colorado Desert, including Coachella Valley and Imperial Valley.

### A. Open desert; indigenous species.

#### Compositae

FRANSERIA DUMOSA		March-April
HYMENOCLEA SALSOLA		Feb.-April
ARTEMISIA TRIDENTATA	Mountain Sage Brush	Sept.-Nov.
Dicoria brandegii		Aug.-Sept.
Chrysothamnus nauseosus varieties	Rabbit Bush	Aug.-Oct.

There is less Chrysothamnus and Artemisia tridentata here than on the Mojave Desert.

#### Chenopodiaceae

ATRIPLEX CANESCENS	Wingscale	May-June
ATRIPLEX POLYCARPA	Allscale	May-June
ATRIPLEX LENTIFORMIS	Lenscale	May-June
Allenrolfea occidentalis		April-May
Suaeda torreyana		Spring
Kochia americana californica		March

#### Grasses. Graminae

Distichlis spicata	Salt Grass	March-June
Bromus rubens	Red Brome	March-April
Hilaria rigida	Galleta Grass	Spring
Triodia pulchella	Frost Grass	Spring
Stipa speciosa	Needlegrass	Spring

# BOTANICAL SURVEY—SMALL AND SMALL

## Other families

<i>Ephedra californica</i> (Gnetaceae)	April
<i>Croton californica</i> (Euphorbiaceae)	March-July
<i>Plantago insularis</i> variations fastigiata and scariosa (Plantaginaceae)	March-May

(B) Irrigated Sections; around towns, farms, habitations.

## WEEDS

AMBROSIA PSILOSTACHYA	Western Ragweed	July-Sept.
AMARANTHUS PALMERI	Careless Weed	May-July
<i>Atriplex lentiformis</i>	Lenscale	May-July
<i>Atriplex canescens</i>	Wingscale	May-June
<i>Chenopodium album</i>	Lamb's Quarters	Spring-Summer

## GRASSES

CYNODON DACTYLON	Bermuda	Spring; Summ., Fall
<i>Elymus triticoides</i>	Wild Rye Grass	April-June
<i>Lolium multiflorum</i>	Italian Rye Grass	April-June
<i>Hordeum vulgare</i>	Barley	Spring
<i>Setaria viridis</i>	Bristle Grass	May-June
<i>Phalaris minor</i>	Canary Grass	April-May
<i>Avena sativa</i>	Oats	Feb.-March

## TREES

<i>Populus fremontii</i>	Cottonwood	March
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Note on the Colorado River Region: Thickets of *Populus fremontii* and *Salix goodingii*, both wind-pollinated, line the banks of the river in the Colorado Desert. There are also vast thickets of *Baccharis scrigiloides* (Compositae) and *Tamarix gallica*. The latter blooms prolifically during a long season.

## VI SOUTHERN END OF THE SAN JOAQUIN VALLEY.

## WEEDS

SALSOLA KALI	Russian Thistle	April-Sept.
ATRIplex POLYCARPA	Allscale	Spring
<i>Atriplex lentiformis</i>	Lenscale	May-June
<i>Atriplex argentea expansa</i>	Silverscale	Spring
<i>Atriplex bracteosa</i>		Spring
<i>Chenopodium murale</i>	Nettle-leaf Goosefoot	April-Dec.
<i>Suaeda moquini</i>		
<i>Ambrosia psilostachya</i>	Western Ragweed	Aug.-Oct.
<i>Franseria acanthicarpa</i>	Western False Ragweed	Sept.-Oct.
<i>Artemisia dracunculus</i>		June-July
<i>Artemisia vulgaris</i> varieties	Mugwort	July-Aug.

## GRASSES

CYNODON DACTYLON	Bermuda Grass	March-Nov.
SORGHUM HALEPENSIS	Johnson's Grass	June-Sept.
ELYMUS TRITICOIDES	Beardless Wild Rye Grass	May-June
<i>Distichlis spicata</i>	Salt Grass	Spring
<i>Avena fatua</i>	Wild Oats	March-April
<i>Bromus rigidus</i>	Ripgut	April-May
<i>Bromus rubens</i>	Red Brome Grass	April-May
<i>Bromus molliformis</i>	Soft Chess Grass	April-May
<i>Hordeum murinum</i>	Fox Tail	March-April
<i>Festuca myuros</i>	Fescue Grass	March-April
<i>Elymus glaucus</i>	Bluc Wild Rye	May

# BOTANICAL SURVEY--SMALL AND SMALL

<i>Poa annua</i>	Wild Annual Blue Grass	Feb.-April
<i>Agrostis</i> species	Bent Grass	Late Spring
<i>Phalaris</i> species	Canary Grass	Late Spring
<i>Stipa</i> species	Needlegrass	April-May

## TREES

<i>Populus fremontii</i>	Cottonwood	March
<i>Juglans nigra</i>	Black Walnut	May-June
<i>Olea europaea</i>	Olive	May-June
<i>Quercus lobata</i>	Valley Oak	March
<i>Quercus wislizenii</i>	Interior Live Oak	March-April
<i>Juglans californica</i>	So. Calif. Black Walnut	April-May
<i>Fraxinus oregona</i>	Oregon Ash	Early Spring
<i>Platanus racemosa</i>	Sycamore	March-April
<i>Salix</i> species	Willow	Feb.-March

## Complete Supplementary List

### 1. Anemophilous plants of unproved antigenicity

Botanical Name	Common Name	Pollinating Date	Area
<i>Cupressus macrocarpa</i>	Monterey Cypress	Feb.-April	I, II, IV
<i>Cupressus guadalupensis</i>	Guadalupe Cypress	Dec.-March	IV, V
<i>Juniperus californica</i>	Calif. Juniper	Dec.-Feb.	IV
<i>Cedrus deodara</i>	Deodar Cedar	Oct.-Dec.	IV
<i>Sequoia sempervirens</i>	Coast Redwood	Dec.-Feb.	IV
<i>Pinus coulteri</i>	Coulter Pine	May-June	III
<i>Pinus jeffreyi</i>	Jeffrey Pine	May-June	III
<i>Pinus ponderosa</i>	Western Yellow Pine	May-June	III
<i>Pinus lambertiana</i>	Sugar Pine	May-June	III
<i>Pseudotsuga macrocarpa</i>	Big-cone Spruce	May	III
<i>Libocedrus decurrens</i>	Incense Cedar		III, IV
<i>Abies concolor</i>	White fir	May-June	III
Palms Species	Palms		IV
(Several ornamental species flowering at different times throughout the year.)			
<i>Phoenix dactylifera</i>	Date Palm	May	V, 2
<i>Juncus acutus</i>	Rush	Spring	II
<i>Typha latifolia</i>	Cat-tail	Spring	II

### 2. Entomophilous and amphiphilous plants of possible antigenicity.

(Most of these occur in quantity over large areas and produce much pollen. The rest are commonly planted ornamentals and street trees.)

<i>Eucalyptus</i> species	Eucalyptus	March-July	II, IV
<i>Ceratonia siliqua</i> *	Carob	Oct.-Nov.	II, IV
<i>Adendostoma fasciculatum</i> *	Chamise	April-June	I, III
<i>Cercocarpus betuloides</i> *	Mt. Mahogany	March	I, III
<i>Cercocarpus ledifolius</i> *	Mt. Mahogany	March-April	III
<i>Larrea tridentata</i>	Creosote Bush	March-June	V
<i>Prosopis juliflora</i> *	Honey Mesquite	April-May	V
<i>Prosopis pubescens</i> *	Screwbean Mesquite	April-May	V
<i>Tamarix gallica</i> *	Tamarisk	March-July	V
<i>Tamarix aphylla</i> *	Tamarisk	April, and Aug.-Sept.	V
<i>Robinia pseudacacia</i>	Locust	April-May	VI
<i>Melia azedarach</i>	Umbrella Tree	Summer	VI, V
<i>Grevillea robusta</i>	Flame Tree	May-July	VI
<i>Cinnamomum camphorae</i>	Camphor Tree	March-April	IV
<i>Brassica campestris</i> and other species	Mustard	Spring	I, II, IV
<i>Eriogonum fasciculatum</i>	Wild Buckwheat	April-August	I, IV
<i>Salvia apiana</i>	White Sage	April-May	I, II, IV
<i>Salvia mellifera</i>	Black Sage	April-May	I, III, IV
<i>Encelia farinosa</i>	Encelia	April-June	V

\*Amphiphilous--both insect and wind-pollinated.

# BOTANICAL SURVEY—SMALL AND SMALL

## 3. Occasional anemophilous plants of known antigenicity.

<i>Acer macrophyllum</i>	Big-leaf Maple	Mar.-April	III., IV.
<i>Acer negundo</i>	Box Elder	Mar.-April	I., IV., VI.
<i>Betula alba</i>	White Birch	Mar.-April	II., IV.
<i>Fraxinus oregona</i>	Oregon Ash	Mar.-April	III., IV.

Botanical determination of plants in these charts is according to the following authorities:

Dr. W. L. Jepson, "Manual of Flowering Plants of California"; "Flora of California"; "Trees of California."

A. S. Hitchcock, "Manual of the Grasses of the United States," U. S. Dept. of Agriculture Publication.

Harvey M. Hall, "The Genus *Haplopappus*."

H. M. Hall and Frederick E. Clements, "Phylogenetic Method of Taxonomy," Carnegie Institution of Washington Publication.

The authors wish to acknowledge the indispensable assistance of Mr. Frank W. Peirson, authority on the flora of the San Gabriel Mountains, in checking our identifications.

<i>Towns</i>	<i>Regions Affecting Towns</i>
Bakersfield.....	San Joaquin Valley
Barstow.....	Mojave Desert
Bishop.....	Owens Valley, Mojave Desert
Blythe.....	Colorado Desert
El Centro.....	Colorado Desert (Imperial Valley)
Indio.....	Colorado Desert (Coachella Valley)
Lancaster.....	Mojave Desert
Long Beach.....	Coastal Plain
Los Angeles.....	Coastal Plain, Coast Ranges, Interior Valleys
Mojave.....	Mojave Desert
Needles.....	Mojave Desert
Palm Springs.....	Colorado Desert
Pasadena.....	Interior Valleys, Interior Ranges
Redlands.....	Interior Valleys, Interior Ranges
Santa Ana.....	Coastal Plain, Interior Valleys, Coast Ranges
Santa Barbara.....	Coastal Plain, Coast Ranges
San Bernardino.....	Interior Valleys, Interior Ranges
San Diego.....	Coastal Plain, Coast Ranges
San Luis Obispo.....	Coastal Plain, Coast Ranges
Santa Maria.....	Coastal Plain
Santa Monica.....	Coastal Plain, Coast Ranges
Ventura.....	Coastal Plain, Coast Ranges
Victorville.....	Mojave Desert

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## BOTANICAL SURVEY—SMALL AND SMALL

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  7. Watry, A., and Lamson, R. W.: A botanical survey of Needles, California. *J. Allergy*, 2:272, 1931.
  8. Wodehouse, R. P.: Hay Fever Plants. Waltham, Mass.: Chronica Botanica Co., 1945.

### IMPORTANCE OF BRONCHOSCOPY IN ASTHMA IN CHILDREN.

Dighiero, J. C.: (Importancia de la broncoscopia en el asma del niño). *Arch. de pediat. del Uruguay*, 16:152-159, March 1945.

The author discusses the importance of bronchoscopy in diagnosis and treatment on the basis of a study of twenty cases, sixteen of which are studied in the intervals between attacks of asthma and four during attacks.

1. Those examined between attacks comprised three groups:

In the *first* group no pathological changes were visible, the mucosa was normal, there were no appreciable secretions or alterations.

In the *second* group there was severe congestion of the tracheobronchial mucosa with hypersecretion, a condition often called "allergic mucosa." The patients with these lesions of the bronchial mucosa were also subject to vasomotor rhinitis and presented personal and familial histories of allergy pertaining to the group of atopic asthma described by Coca.

Finally, a *third* group of cases showed changes resembling chronic tracheo-bronchitis. The mucosa was thickened, pale, dull, covered with mucopurulent secretions. There were also bronchial changes characterized by flaccidity, loss of elasticity, and limitation of movements of expansion and retraction. This flaccid state creates a favorable condition for emphysema.

Differential diagnosis between asthma complicated by bronchial infection and chronic tracheobronchitis with attacks of asthmatic dyspnea can be made only through the clinical history and antecedents of the patient. Treatment of the bronchial infection should be an integral part of the treatment. In such cases the author has had good results from repeated bronchial aspirations, bronchoscopic instillation of sulfonamides, topical applications, et cetera and, in cases where there was no great obstruction, from pulmonary nebulization, with sulfonamides or iodized oil. In addition to these local measures he advises general treatment and anti-allergic measures in cases of specific sensitivity.

2. Only four patients were studied during attacks. One case is described in some detail: that of a fourteen year old girl who had suffered from asthma since she was four years old. In all the cases examined there was congestion and edema of the mucosa, reducing bronchial permeability. The congestion was not equal in all cases, being more accentuated in patients in whom the mucosal congestion was of an allergic nature. These lesions were accompanied by thick, viscous secretions, mucous or mucopurulent. There were also changes in the tracheobronchial movements, varying with the degree of dyspnea and the tonicity of the bronchial walls. Bronchoscopically, bronchial spasm was not seen, although it has been noted by others. The changes that were actually observed were sufficient to explain the dyspnea and the difficulty of breathing characteristic of asthmatics.

When congestive lesions of the mucosa, as seen in allergic asthma, prevail the attacks start suddenly and rapidly become intense, but they yield readily to adrenalin. On the other hand, when there is bronchial infection and changes in the tone and elasticity of the bronchi, the attacks are milder but much more prolonged; they respond very little if at all to adrenalin, and between attacks the patient is subject to wheezing, especially at night and finally a permanent form of asthmatic breathing.

Bronchial aspiration, combined with bronchial insufflation of oxygen, is an emergency treatment in all cases of serious asthmatic attacks with asphyxia and cyanosis, in which other treatment has failed.

J. G.

## CHROMIDROSIS ASSOCIATED WITH RAGWEED HYPOSENSITIZATION

HELEN C. HAYDEN, M.D., F.A.C.A.

Decatur, Illinois

CHROMIDROSIS is a rare disorder of unknown cause characterized by the excretion of colored sweat. The perspiration may be tinged yellow, red, green, blue, or black, and may appear in this form; or it may develop color by oxidation in the air; or it may unite with substances on the surface of the skin to produce the abnormal color.<sup>3</sup> The most common forms are cyanidrosis and melanidrosis, terms indicating blue and black sweating, respectively. The bluish color is thought to be due to the excretion of indoxyl or one of its derivatives which is oxidized to indigo. The indoxyl derivative originates in the intestinal tract. Colored sweat, in some instances, has been due to the ingestion, or absorption by contact, or inhalation of certain substances such as potassium iodide, copper, iron, et cetera. Most reddish sweats, such as those seen in the axillary region, are due to the action of chromatogenic bacteria and are known as pseudochromidrosis. Murray<sup>2</sup> reported golden yellow perspiration and even yellow tears in a patient due to the absorption of a dye from face powder. The condition cleared up promptly two days after the use of the face powder was discontinued. Chromidrosis tends to appear in neurotic women, and frequently there is a history of a pelvic disorder. As a rule, hyperidrosis is not present.

The following case report is of interest:

Miss F. L. E., fifty-eight years of age, who has suffered from grass and ragweed pollinosis for forty-six years, associated with asthma for ten years, reported May 14, 1940, for grass and ragweed hyposensitization. There was nothing of note revealed at the physical examination with the exception of a few sibilant râles in both lungs. There was 4 per cent eosinophilia. There were large positive scratch reactions to giant and short ragweed, and burweed marsh elder; and positive intradermal reactions to grass pollen extract and house dust. Intradermal food tests were discontinued because of the excessive number of positive reactions but, by diet trial, the patient was found clinically sensitive to milk, rye and egg. Preseasonal ragweed hyposensitization was started, and later coseasonal grass hyposensitization was given with good results during the grass season and fair results during the ragweed season of 1940.

For the past eight to nine years this patient has noticed that about August 15 each year a "smudgy" bluish discoloration has appeared on her wash cloth. It begins gradually at the onset of the ragweed season and becomes more intense toward the peak of the season and gradually disappears by frost. Since 1941, dust hyposensitization has been given perennially, and preseasonal grass and ragweed hyposensitization has been repeated each year. A maximum dose of 5,000 units of grass has afforded excellent protection, while a maximum dose of 100 units of ragweed extract is all that tolerance permits. General reactions in the form of asthma occurred when this dose was exceeded; nevertheless, it has afforded fair

## CHROMIDROSIS—HAYDEN

protection. Every year until this year, however, the discoloration of the wash cloth would begin with the advent of the ragweed season and continue until frost. It is not known whether this condition would occur in the absence of treatment, as injections of ragweed pollen extract have been repeated each year since 1935 because of the definite benefit afforded.

In 1945, without any alteration in the treatment schedule, the discoloration began about June 10, six weeks after ragweed hyposensitization had been started, when injections were given biweekly and a dosage of only 5 units had been reached. Following this, during an interval of two weeks, when no injections were given, the discoloration almost disappeared but reappeared in less intense form when injections were resumed at weekly intervals. For the past two years it has been impossible to exceed a dosage of 12 units of ragweed extract without inducing asthma, and yet the clinical results have been better than in previous years on a higher dosage. The bluish tinting continued all during the summer of 1945 in mild form but became markedly accentuated late in August and during the first two weeks in September and as usual disappeared by frost. Injections of ragweed extract were discontinued for the year on August 23, 1945.

### COMMENT

During the time when the wash cloths are stained there is no discoloration seen on the skin or clothing or handkerchiefs, and there is no abnormal amount of perspiration. The wash cloths turn a deep inky blue when wet and impart to the water a slightly bluish tint. Later, the color turns blackish and remains so unless the cloths are boiled and bleached. Most of the color seems to come from the face, especially about the eyes, with lesser amounts from the axillary regions and groins. The amount of perspiration is a factor inasmuch as the discoloration is more marked in very hot and humid weather. It is difficult to understand why the discoloration began in June, 1945. It was unusually cool and rainy during this time, there was no excessive perspiration, and the dosage of ragweed extract was comparable to that given the year before. This patient is nervous, conscientious, and rather discontented. She had a myomectomy many years ago, but no menstrual difficulties followed and later there were no untoward menopausal symptoms.

No studies were made of the urine, but Dr. Smith Freeman of Northwestern University School of Medicine extracted from one of the wash cloths a blue substance that behaves chemically like indigo. Indican, which is a precursor of indigo, is a normal constituent of the urine. Indigo may exist in a blue or oxide form, or in a colorless or reduced form. It is possible that in this patient indigo was excreted in the colorless form and that the oxygen of the air or the chlorine contained in water may have initiated its conversion into the oxidized or colored form. Indole and skatole are formed normally in the large intestine and are due to the deamination and decarboxylation of tryptophane by bacterial action.<sup>1</sup> Most of the indole is eliminated in the feces but small quantities are absorbed into the blood stream and are detoxified in the liver by conjugation with sulfuric acid and potassium or with glycuronic acid to form

*(Continued on Page 387)*

## ALLERGIC CAUSES OF PRURITUS ANI

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Wharton, Texas

THE following is a presentation of fourteen cases of pruritus ani seen by our allergy department. Most of these cases had been previously treated unsuccessfully by many methods, and show clearly that allergy is an important, neglected primary cause of pruritus ani.

The role of allergy in the production of pruritus ani has been described in a meager fashion for many years. It is not the intent of this paper to deprive the proctologists of their field of work. However, it is the intent of this paper to enjoin their co-operation in securing relief of a condition which is embarrassing, uncomfortable, and at times disabling. There has been very little literature associating pruritus ani with allergy. There has been only slight acknowledgment of the etiological relationship of allergy and pruritus ani in many commonly used textbooks on this subject to date. By definition, pruritus ani is an entity which subjectively consists of chronic or recurrent itching in the perianal region. The objective findings are usually excoriation, edema, thickening of the skin, and exudation in most cases. All of these, however, vary in degree and intensity.

Patients who have consulted us for relief of this symptom complex complain worse at night and have cycles of improvement and exacerbation. They have usually tried medications both locally and orally, some of these prescribed by the physicians and others by their neighbors. Many have tried x-ray, rectal dilatations, local injections, tattooing of the anal skin with anesthetics of protracted action, and many other surgical and semi-surgical procedures.

It is desirable to emphasize to you that this presentation is intended not only to place a large number of these conditions in their proper places from an etiological standpoint, but to simplify their therapy after having once determined their etiology. Much has been written regarding the presence of pH alterations (Slocumb<sup>5</sup>), (Davis<sup>4</sup>); mechanical factors (Buie<sup>1,2</sup>); chemical disturbances (Tucker<sup>6</sup>). We maintain that we have frequently observed changes which we originally felt were primary to be secondary to allergy.

The best classification from the standpoint of etiology is taken from Cantor's<sup>3</sup> paper. It is introduced to give you the present scope of the extensiveness of causes.

As we review the classification dealing with cryptogenic pruritus ani, local, psychogenic, traumatic, thermal, chemical and other types of rectal diseases, it is certainly difficult at times to place them as a primary cause. Even the presence of local growths of yeast, fungus, and *Trichomonas* can be predisposed to by the presence of weeping, allergic eczemas of the anus.

## PRURITUS ANI—RUGELEY

### SPECIFIC ETIOLOGICAL CLASSIFICATIONS

- A. Cryptogenic pruritus ani—usually associated in vicious cycle with relief trauma (i.e. scratching)
- B. Local Rectal
  - 1. Rectal constipation
  - 2. Fissure
  - 3. Fistula
  - 4. Cryptitis and papillitis
  - 5. Proctitis
    - Factors
    - Mechanical (Traumatic)
    - Chemical
    - Bacterial, *with later possibility* of allergic and psychogenic complicating factors
- C. Psychogenic
  - 1. Hysteria
  - 2. Anal masturbation
  - 3. Other psychoses
- D. Traumatic
  - 1. Scratching Mechanical
  - 2. Rubbing of clothing Mechanical
- E. Allergic
  - 1. Sensitization to bacterial toxins, fungi, or focal infections
  - 2. Foods
  - 3. Drugs, et cetera
  - 4. Eczemas
- F. Parasitic
  - 1. Pinworms
  - 2. Trichomonas
  - 3. Monilia
  - 4. Fungi
  - 5. Itch mites
- G. Thermal—warmth and associated perspiration (moisture)
- H. Chemical
  - 1. Chemical in diapers (washing): Infant pruritus
  - 2. Alkaline or acid urine
  - 3. Self or prescribed medications
  - 4. Sweat
  - 5. Urine containing calcium or oxalate crystals
  - 6. Urine of senile dribbling
- I. General Metabolic
  - 1. Thyroid dysfunction
  - 2. Diabetes
  - 3. Kidney disease
  - 4. Liver disease
  - 5. Anemia
  - 6. Vitamin deficiencies
- J. Reflex (?)

TABLE I

	DURATION AND PREVIOUS TREATMENT	SOURCE OF ALLERGEN SUGGESTED BY	STUDIES	CONFIRMATION AND TREATMENT
Case 1. W.W. Male 30 yrs. 2-3-39	4 yrs. intermittent Medicine & x-ray Dilatation Alcohol injection Hemorrhoidectomy	History	Not done	Elimination diet Proved fish
Case 2. R.A.M. Male 32 yrs. 2-3-39	2 mos. intermittent Medicine X-ray	History	36 food tests all less than 2+ Blood eosinophilia Avocado patch test pos. at 4th day. Neg. 48 h.	Proved by elimination and inclusion. Patch test remained positive for several weeks.
Case 3. W.L. Male 29 yrs. 4-21-43	9 yrs. intermittent Medicine, x-ray Rectal dilatation	Routine studies	30 foods and 6 misc. Pork 3+, beef 3+ 4 other 2+ pH 7.8 Eosino. 3+ pH 7.8	Elimination diet proved beef
Case 4. G.C.S. Female 35 yrs. 5-25-43	20 yrs. constant Injection of hem. Fistula operation Medicine & diet Colonic irrigation	Routine studies	82 foods Wheat 2+, prunes 2+ Apples 2+, green peas 2+	Patch test pos. after 5 days. Symptom free 2½ years
Case 5. E.A.F. Female 44 yrs. 5-30-43	2 to 3 mos. Medicine locally	Routine studies History	34 foods—dewberries 4+ Beef 3+, w. potatoes, beets, yeast 2+ Eosino. +, pH 8	Elimination diet No recurrences Yeast in sinews cleared up without local treatment
Case 6. F.R. Age 35 yrs. 7-4-43	2 yrs. seasonal Medicine	History Migraine for 1 yr.	20 foods—figs, wheat 3+, Others 0	Diet proved figs. Migraine due to chocolate, fish and onions. Patch: acetone neg. Water pos. 3 days.
Case 7. G.S.R. Female 43 yrs. 4-14-44	10 yrs. constant (Pt. ashamed to tell doctor.) Medicine	History Eczema on hands	40 tests. Six 3 & 4+ reactors. Mold, H.D., staph. & pyreth. 3 & 4+ pH 7.6, cosino. pos.	Diet proved chicken 2+, string beans and rice 3+, Eczema and pruritus ani healed simultaneously.
Case 8. J.F.Mc. Male 74 yrs. 5-18-44	Constant 1 mo. None	History of Rx. Dysuria (associated)	10 foods 9 were 4+ 1 was 3+ Apexol—1+ patch test after 4 days	Elimination diet—no relief Sensitive to all C.L.O. Patch test pos. 3 weeks

TABLE I. (continued)

	DURATION AND PREVIOUS TREATMENT	SOURCE OF ALLERGEN SUGGESTED BY	STUDIES	CONFIRMATION AND TREATMENT
Case 9. L.L.H. Male 27 yrs. 10-14-44	3 years constant Medicine	Routine studies	21 skin tests Spinach 3 + 6 others 2 + Potatoes 2 + Eosinophiles pos. pH 8	Elimination diet proved potatoes Patch test pos. after 48 h. Present for 3 more days
Case 10. R.J. Male 37 yrs. 1-10-45	3 or 4 years Occasionally Medicine	History	20 foods all 1 + or neg. Patch test for peanut oil pos. 48 h.	Elimination and inclusion
Case 11. W.E.T. Female 38 yrs. 1-23-45	Many years Constantly Medicine	History and relief after colostomy Later eczema on abd. Patient blamed milk	Skin tests not done	Elimination and inclusion proved cause to be milk
Case 12. G.H. Male 43 yrs. 2-5-45	In summer for 2 or 3 years Medicine	Worse when feet had "athlete's foot"	20 foods negative Contactants negative Trichophyton 3 + Eosinophiles positive Fungus neg. locally	Feet treated Trichophyton desensitization Patient relieved
Case 13. G.P. Male 44 yrs. 9-3-45	5 mos. constant Medicine Injection hem. Hemorrhoidectomy X-ray therapy	Routine studies	11 foods Beef 3 + Egg 3 + Others 1 or 2 + Eosinophiles pos. pH 7	Elimination diet confirmed eggs
Case 14. V.B.H. Male 44 yrs. 10-7-45	Duration 6 years const. Medicine Hemorrhoidectomy Fistula operation X-ray therapy	Routine studies	30 foods tested Most of them 2,3,4 + B. Coli 4 + Eosinophiles pos. pH 7.2	Elimination diet gave no relief Sulfaguanidine—improved Desensitization gave most relief

## PRURITUS ANI—RUGELEY

The anal skin is most often moist, excoriated and incompletely cleansed, and this makes it ideal for entrance of antigen into the skin.

In our more recent cases, we have made the following routine studies:

1. Careful history of the condition with reference to duration of symptoms, the type of diet, medicines, infections and other allergic exposures.
2. Proctoscopic and prostatic examination, including study of prostatic exudates.
3. Rectal smears for eosinophiles, determination of relative pH by the use of litmus paper, scrapings for worms and microscopic examination for the presence of yeast, molds and trichomonads.
4. Complete blood count, blood Wassermann, urine and stool.
5. Allergic survey, being careful to rule out all contactants in addition to ingested allergens.
6. The careful use of food diary and diets to eliminate or incriminate the suspected food.

The presentation of cases in Table I represents only a small series and is not presented for statistical value. At the same time, without exception, these cases have represented the ultimate success in management of fourteen cases after all other measures have failed. In investigating some of the earlier cases, it will be noted that some of the procedures which are routinely carried out at this time were omitted. That was due in part to our lack of understanding of the causes as we now see them. Please note that in a large number of cases the patient has suggested the offending allergen.

To summarize the conclusions which may be drawn from the above cases:

1. Careful attention to history is an important diagnostic help.
2. Elimination diet, food diary and trial and error investigation must be resorted to in every case.
3. The skin tests appear helpful in some cases, and latent reactions are more significant than early reactions.
4. Pruritus ani may be a contact condition, as suggested by patch tests and the colostomy patient.
5. Exudates from anal margins contain many eosinophils when allergic causes are present.
6. Allergic causes of pruritus ani should be investigated before radical procedures are suggested, such as surgery, x-ray, injections, division of nerves or tattooing of the anal margins with anesthetics.
7. Diagnoses of psychogenic and neurotic etiology are often erroneous.
8. Cryptitis, papillitis, pH changes, fissures are often secondary instead of primary changes.

*(Continued on Page 396)*

## THE QUANTITATIVE LEPROMIN TEST IN LEPROSY

M. SALAZAR MALLEN, M.D., F.A.C.A. and L. ROSAS PRIETO, Ph.D.  
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THE lepromin test was described by Mitsuda in 1923. Since then numerous works have been published dealing with its value in the diagnosis and prognosis of leprosy. With regard to the first point, there have been many discussions concerning the immunological character of the response and its specific or non-specific basis, the relative value of early readings (twenty-four to forty-eight hours) or late ones (seven, fourteen and twenty-one days) and finally the relative importance of the morphological characteristics of the cutaneous response itself (erythema, nodule, necrosis).

The aim of the present work is to analyze the reactions observed in normal non-lepers, as well as in lepers of the different forms, following the intradermal injections of lepromin in different dilutions (quantitative reaction), care being taken to record the reaction during the first twenty-four to forty-eight hours and at seven, fourteen and twenty-one day intervals recording all skin changes—observed (qualitative reaction).

### MATERIAL AND METHODS

1. In preparing Mitsuda's antigen, Muir's modification was followed, nodules were obtained preferably from the ear lobe of leprosy patients of the lepromatous form. The nodules were boiled in water for twenty minutes, cut into small fragments and the epithelium removed.

The material was dried in the air current of an electric fan for several hours and then placed in a dessicator and dried over concentrated sulphuric acid. When completely dry, the material was powdered in a mortar and kept dry, sufficient material having been prepared to insure uniformity in the results throughout the experiment.

2. Suspension of the antigen was made as follows: 400 mgms. of the dry powder were triturated with 10 c.c. of saline solution, the suspension drawn off, and the residue was again triturated with the same amount of saline and the resulting suspension again drawn off. This process was repeated three or four times. The pooled suspension was shaken in a flask and allowed to settle for ten minutes, the liquid decanted and the sediment set aside. The volume was made up to 100 c.c. with saline and phenol 0.5 per cent. The antigen thus obtained was bottled and sterilized by autoclaving at 120 C. for thirty minutes. Using sterile technique, dilutions of the original antigen in saline were made to obtain suspensions at 50 per cent, 20 per cent, 10 per cent and 1 per cent. Part of the undiluted antigen was set aside to be used as a 100 per cent suspension.

3. Intradermal tests were made by injecting 0.1 c.c. of the above dilutions in the outer aspect of the arm, separate syringes being used

for the different concentrations. The concentrated (100 per cent) antigen was always injected into the upper part of the arm, and the dilutions in decreasing strength in corresponding lower positions.

#### 4. Recording of skin responses:

Individuals were observed twenty-four and forty-eight hours following injection and at intervals of seven days over a period of three weeks. Infiltration was measured with a millimeter scale and the morphological alterations such as pustules or necrosis were recorded. Hayashi was the first to try to standardize and correlate the degree of reactivity from slight to strong reactions, with nodules from 2 mm. to more than 10 mm. and formation of pustules. Rothberg studied some 1,000 lepers and stated that positives (meaning immunological defense) should be accepted only if nodules of more than 5 mm. were formed at the end of the third week. In our work, any significant change in the skin response was recorded and a positive reading was taken to be any infiltration greater than 1 mm. in diameter.

Studies were made along the above lines in forty-six "healthy" non-leprous adults of both sexes taken from the wards of the General Hospital, and sixty lepers, thirty-nine of which were of the lepromatous and twenty-one of the tuberculoid form. The clinical study of the patients was kindly made by the medical staff of the Dr. Pedro López Dispensary for Lepers of Mexico City.

### RESULTS

The result obtained in the "healthy" group, are clearly demonstrated in Figure 1.

Readings made in forty-eight hours revealed 97.8 per cent positives with the concentrated antigen. The mean was 6.8 mm., necrosis was noted in 4.4 per cent. Positivity decreased to 32.6 per cent with the 1 per cent antigen (mean 3 mm.). No necrosis was observed from the dilutions. Late readings (seven, fourteen and twenty-one days) were somewhat less positive but necrosis was higher reaching: 7.7 per cent (seventh day), 18.9 per cent (two weeks) and 20 per cent (three weeks) with the full strength antigen.

The lepromatous lepers (thirty-four cases), behaved quite differently. The concentrated antigen gave 79.5 per cent positives in forty-eight hours. The mean was 7.2 mm., necrosis was noted in 33.3 per cent, but quantitatively a response was observed with difficulty in using the 10 per cent antigen. No reactions were observed after injecting the 1 per cent antigen (Fig. 1). On the seventh day, more striking results were observed. There was a decrease in the size of the previous papules, and there was no local reaction to the 20 per cent antigen.

Readings taken on the fourteenth day gave only one positive to the 100 per cent antigen consisting in a five mm. nodule with necrosis. This

## LEPROMIN TEST—MALLEN AND PRIETO

same case was the only positive on the twenty-first day, the nodule having acquired a size of 6 mm. No responses were elicited from the antigen dilutions during these two periods of observation.

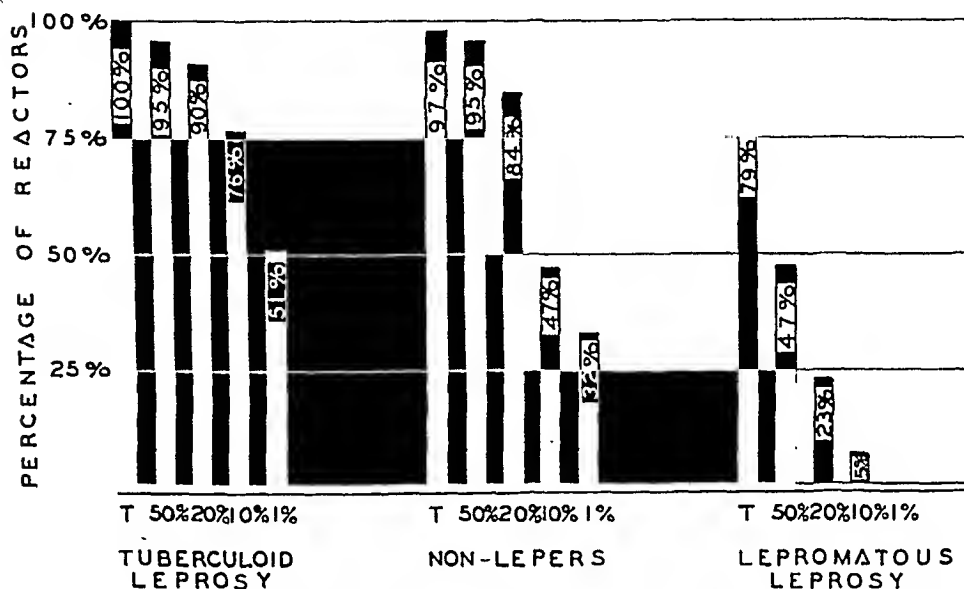


Fig. 1. Mitsuda reaction—readings at forty-eight hours. Quantitative responses in the different groups of leprosy and in non-lepers.

The most interesting results were obtained in the tuberculoid form of leprosy as shown in the Figure 1. There were 100 per cent positives to the concentrated antigen in the forty-eight-hour interval with a mean of 9.2 mm. Necrosis was observed in 14.2 per cent and 10 per cent with the 100 per cent and 50 per cent dilutions respectively. There were 57 per cent positives obtained using the 1 per cent antigen dilution with a mean of 5.2 mm. The erythema observed in the forty-eight-hour reading groups was marked and pustules were frequent. On later readings, infiltration was attenuated but the incidence of necrosis increased to 70 per cent with the concentrated antigen in the three-week period. Necrosis was evident in 20 per cent of the individuals after reaction to the 1 per cent antigen at the same time interval.

### DISCUSSION

From the data presented it is readily observed that the Mitsuda test behaved in an entirely different manner in tuberculous and lepromatous individuals regardless of the time when readings were taken. Authorities agree on this point, but many physicians hesitate to concede any value to the twenty-four to forty-eight hour responses stressing the morphological (qualitative) changes observed typically in later observations (nodules, pustules, and necrosis). In our cases, however, a clearcut difference was

## LEPROMIN TEST—MALLEN AND PRIETO

observed between the tuberculoid and lepromatous patients when readings were taken at forty-eight hours. Figure 1 shows that with the quantitative test, lepromatous patients failed to react to the 1 per cent dilution, while in the tuberculoid individuals, 50 per cent positives were obtained with

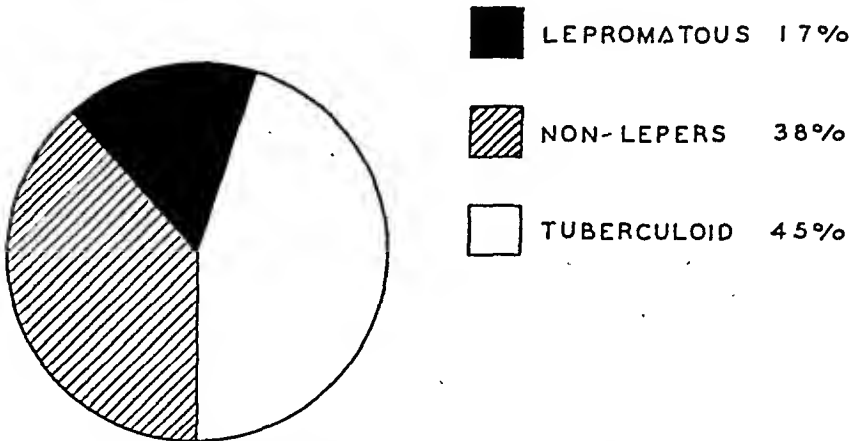


Fig. 2. Mitsuda reaction—readings at forty-eight hours. Qualitative measure (area of positive skin response) or reactions at forty-eight hours in the different groups of leprosy and in non-lepers.

the same antigen dilution. It may also be seen that the percentage of positives ranged from 100 per cent (tuberculoid) to 79.5 per cent (lepromatous), using the concentrated antigen. The 10 per cent antigen resulted in 76 per cent and 5.8 per cent positives in the tuberculoid and lepromatous cases respectively.

If one considers the size of the responses as observed in the 48 hours reading and expresses the sum of the average mean in each group of individuals taken in percentages, the result as seen in Figure 2 leaves little doubt as to the larger skin area response of the tuberculoid group.

The response in normals, considered positive in many cases by most authorities is quantitatively and qualitatively more intense than in lepromatous cases. Thus it may be assumed that the early, twenty-four to forty-eight hours, responses, drawing an immunological parallel with the tuberculin test, could be interpreted as strictly specific to reveal primary sensitization. Then non-lepers would give the normergic positive response while tuberculoid patients would represent the hyperergic individuals, lepromatous then being the hypoergic or anergic group, low response and tendency to necrosis (33 per cent) being comparable to that seen in cases of some skin negative tuberculoids with anergy (negative tuberculin papulo necrotic tuberculids).

### CONCLUSIONS

1. A study was made of the Mitsuda reaction principally in its early forty-eight-hour manifestation. The clinical material consisted of forty-

## LEPROMIN TEST—MALLEN AND PRIETO

six non-lepers, and sixty lepers, thirty-nine of which were of the lepromatous and twenty-one of the tuberculoid form.

2. Quantitative tests were conducted using the antigen in dilutions ranging from 100 per cent to 1 per cent. The morphology of the reaction was considered as a qualitative response.

3. The tuberculoid patients responded in over 50 per cent of the cases to the 1 per cent antigen, the weakest employed. Non-lepers reacted in one-third of the cases, while lepromatous patients failed to react to the same dilution.

4. There is a strict correlation between the intensity of the early, forty-eight-hour response and the late (two or three weeks) development of the necrotic reaction.

5. The average mean diameters of responses seen at forty-eight hours with the 20 per cent antigen dilution were as follows: 3.7 mm. for non-lepers, 2.8 mm. in lepromatous patients, and 10.2 mm. in the tuberculoid forms.

6. It is proposed that if the response obtained in forty-eight hours in non-lepers is taken as normergic, tuberculoids should be considered as hyperergic and lepromatous individuals as hypoergic reactors.

7. Adopting the above criteria for the Mitsuda reaction, there should be no difficulty in considering the same as within the group of the tuberculin (infectious) type of allergy.

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### COLLEGE REGIONAL SPRING CLINICAL COURSE IN ALLERGY

The Mississippi Valley Sectional Instructional Course in Allergy for physicians wishing to refresh their knowledge of the subject and those training for specialization in Allergy will be held under the auspices of the University of Kansas School of Medicine, Kansas City, Kansas, May 5-7. The hours will be from 9 to 12:15 and from 2 to 5:15. This course is for the purpose of acquainting physicians with the fundamentals of diagnosis and treatment of allergic diseases. There will be a round table discussion and every phase of allergy will be presented. The schedule, faculty and detailed information will appear in the November-December *ANNALS*. The fee is \$35.00.

For details write to Dr. Orval R. Withers, Suite 1418 Bryant Building, Kansas City 6, Missouri.

## CONTACT DERMATITIS FROM JAPANESE RIFLES

LT. FRANK HINMAN, JR., MC, USNR

A Japanese rifle was secured for each of ship's company during the stay of this aircraft carrier in Tokyo Bay. These were distributed during a three-week period. An estimated 150 recipients refinished the stocks of their guns, using scrapers and sandpaper. Gloves were not worn and hands were merely washed with soap and water. Seven officers and men subsequently suffered skin lesions severe enough to consult the medical department; of these, two required hospitalization in sickbay. The incidence of dermatitis among those exposed was slightly over 4.5 per cent.

### CASE REPORTS

*Case 1.*—A twenty-two year old pilot had a history of marked sensitivity to poison ivy allergens with a decrease after desensitizing injections, of a recent severe episode of poison oak dermatitis, and of hives on eating shellfish. He sanded his rifle while dressed in shoes, shorts, and skivvie shirt. Two days later he noted a vesicular eruption on the palms of his hands and between the fingers, followed by a similar eruption over the elbows, in the antecubital fossae, on the thighs, and over the ankles. The lesions closely resembled poison oak dermatitis in their grouped vesicles and severe itching. The patient was treated with warm magnesium sulfate soaks and was discharged in five days fit for duty.

*Case 2.*—A thirty-eight year old gunnery lieutenant commander stated that he was very susceptible to poison ivy dermatitis, as were his parents and brothers. Two days after sanding his rifle, he noted persistent itching, then the formation of vesicles on the palms and between the fingers of both hands. These lesions subsequently oozed, then became crusted and edematous. He was treated with plain calamine lotion and was well after six days.

*Case 3.*—A twenty-two year old lieutenant had a history of hay fever every summer from common pollens, and had had occasional eruptions from contact with poison oak leaves. His sister had bronchial asthma. A little more than two days after he sanded his rifle, he noted the typical itching vesicular lesion on the palm, dorsum, and between the fingers of each hand, similar to that he had seen develop on the hands of his shipmate, Case 2. The lesion was treated with calamine lotion without phenol, and although the swelling was marked, it cleared in eight days.

*Case 4.*—This twenty-five year old Chief Machinist's Mate had always been very susceptible to poison oak allergens. He stated that just walking near the plant was sufficient to cause dermatitis. Two days before being seen, he was sanding rifles. The following day he noted a vesicular eruption between the fingers of both hands and on the flexor surface of the left forearm, accompanied by severe itching. The lesions were treated with calamine lotion and cleared after five days.

*Case 5.*—A twenty-four year old lieutenant had had occasional attacks of moderately severe dermatitis from contact with the poison ivy plant, but there was no other history of allergy in himself or his family. Two days before the onset of the lesion, his roommate sanded his gun and distributed varnish about the room.

## CONTACT DERMATITIS—HINMAN

The patient believes that he inadvertently rubbed some of it onto his face. The lesion appeared on the cheeks beneath the eyes, was slightly vesicular, and was accompanied by itching and marked edema. Without approval of a medical officer, he was treated for one day with ammoniated mercury ointment, which caused the

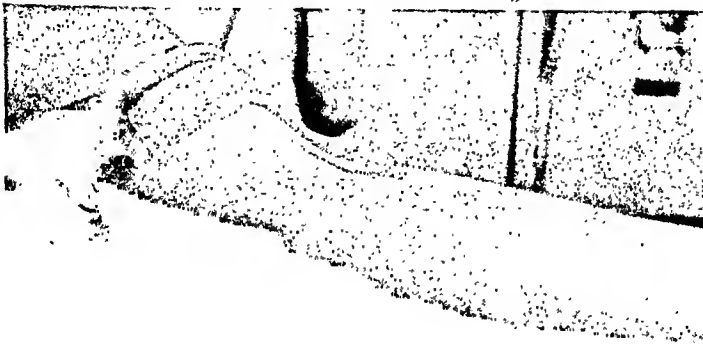


Fig. 1. Case 4: The distribution of the characteristic vesicular lesions is readily seen on the far right.

Fig. 2. Case 4: Grouped vesicles on the flexor surface of the left forearm.

lesion to spread. Warm magnesium sulfate soaks were begun, with application of calamine lotion in the intervals, and the lesions subsided in 10 days.

*Case 6.*—A twenty-two year old second-class aviation ordnanceman stated that he had hay fever every summer and was very susceptible to poison ivy allergens. For three days he took apart and reassembled his rifle, without sanding. The day after completing this, he noted a vesicular rash principally between the first and second digits of his left hand, in the web space. Similar smaller lesions appeared in the web spaces between the second and third, and the third and fourth digits of the left hand. His right hand remained normal. The eruption was treated with calamine lotion and cleared after six days.

*Case 7.*—This twenty-four year old pilot had severe ivy poisoning as a child, but stated that he had not been exposed since. Every fall he had had allergic rhinitis. His only sister is sensitive to poison ivy allergens and experiences "rose fever." He sanded his rifle while fully dressed and two days later he noted a



Fig. 3. Case 6: Typical vesicles in the web spaces.

vesicular lesion on the flexor surfaces of his wrists, and later developed similar lesions about the axillae, ankles, genitalia, and knees. He had changed his clothes several times in the stateroom in which sandpaper dust had settled. The eruption, so severe that hospitalization was necessary in sickbay, was treated with continuous warm wet packs and cleared in six days.

#### REPORT OF CONTROLS

Seven men who worked in the ship's armory and therefore had been cleaning and handling these rifles during the period under study, were interviewed. None of these men had noted itching or eruption. They had had no previous attacks of poison oak dermatitis (except two who had it only as small children) and no history of allergic disease in themselves or their families. Hospital corpsmen, selected for negative allergic histories, were observed refinishing rifles without incidence of dermatitis.

#### DISCUSSION

This outbreak apparently represented the result of intimate contact with a special varnish in individuals with known sensitivity to certain allergens. In Japan, the common natural varnish is obtained from the sap of *Rhus vernicifera*, a species of sumac. The varnish implicated in the present episode has not been positively identified as sumac varnish, although the high incidence of history of sensitivity to the related *Rhus toxicodendron* is suggestive. Before the war, medical officers of ships stationed in China observed that contact with new lacquerware by seamen on liberty caused a similar vesicular dermatitis, known locally as "Ningpo Poisoning." The

itching, vesicular nature of the lesion, its characteristic distribution on the hands and other sites of contact, its onset two days after a definite and usually single exposure, and its response to removal of the exciting agent and to mild treatment indicates that the Japanese varnish on the rifles caused a contact dermatitis.

Patch tests were not performed because of the evidence that the varnish was the etiological agent and because the approach of the ship to the continental United States made the possibility of exacerbation of the disease inadvisable.

#### SUMMARY

Seven cases of itching vesicular dermatitis, usually on the hands and forearms, occurring two days after intense exposure by sensitive individuals to the sanded varnish of captured Japanese rifles, have been observed during a two-week period. The lesions responded readily to removal of the allergen and local treatment. Since many of these rifles are in the hands of men returned from overseas, scattered cases will probably be seen throughout the country. Care should be used by individuals with known sensitivity to plant and other allergens, and that of poison oak or ivy in particular, when handling articles coated with Japanese lacquer or varnish.

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### Chromidrosis Associated with Ragweed Hyposensitization

*(Continued from Page 373)*

potassium indoxyl sulfate or indican which is excreted in the urine. There is no reliable evidence that indican, even in relatively large amounts, produces any signs of toxicity. Amounts given by mouth greatly exceeding those present normally in the bowel produce no symptoms.

The discoloration of the perspiration in this patient is probably due to indigo. The question arises as to whether this reaction is peculiar to this patient or whether it may be present in other patients to a minor degree.

#### SUMMARY

A case of chromidrosis is reported occurring in a patient with ragweed pollinosis during the course of ragweed hyposensitization.

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I wish to express my grateful appreciation to Dr. Smith Freeman, Department of Physiology, Northwestern University School of Medicine, for his aid.

# ALLERGIE

C. VON PIRQUET

Vienna, Austria

IN recent years a series of facts has been collected which belongs to the realm of immunology but which, however, does not fit well into this category; these are the discoveries of hypersensitivity in the immunized organism.<sup>1</sup>

These two terms are blatantly contradictory. When we speak of immunity we think of an organism protected against a disease. How is it that he simultaneously should be hypersensitive to the same disease?

This contradiction was already felt by von Behring when he designated as a "paradoxical reaction" the death of animals, previously highly immunized against tetanus, from small doses of the same toxin.

A "paradox" of course, could only be accepted as an exceptional occurrence; the more, however, one investigates the subject the more he realizes the regularity of this phenomenon. By this time we know already a great number of pathological conditions where symptoms of hypersensitivity are encountered. To this group belong: Tetanus (von Behring, Kretz). Tuberculosis (Courmont, Strauss and Gamaleia, Babes and Proca, Detre-Deutsch, B. Schick, Lowenstein and Rappaport, Moller, Lowenstein and Ostrowsky). Syphilis (Finger and Landsteiner). Diphtheria (Rigt). Serum (Arthus, von Pirquet and Schick, Lehndorff, B. Otto, Rosenau and Anderson). Bacteria in general, organ extracts, various proteins, hay fever (A. Wolff-Eisner).

Is it true that immunity and hypersensitivity are actually combined with one another or are the processes in which previous treatment causes immunity to be separated from those in which it leads to hypersensitivity?

A. Wolff-Eisner<sup>2</sup> intends to carry through the distinction as follows: processes in which toxins are involved lead to the production of antitoxins and immunity; processes in which endotoxins represent the effective agent lead to hypersensitivity.

We see, however, from the experiences with tetanus that hypersensitivity may occur even in exclusively antitoxic processes. The objection of Wolff-Eisner that this is only an exceptional occurrence does not appear to me to touch the essential problem.

Richet<sup>3</sup> who was the first to ascribe an important significance to hypersensitivity which he called anaphylaxis found that injection of an actinium poison produced simultaneously immunity and anaphylaxis: If the injection of the poison was repeated after a certain time interval, the animals usually met with a sudden death. However, if they lived through the

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June 1946, marking the fortieth anniversary of the appearance of the original article.

first shock then they overcame the disease more rapidly than control animals injected but once.

Similar ideas were developed by von Pirquet and Schick<sup>4</sup> concerning serum sickness. The phenomena following reinjection show a more violent and more rapid course.

Recently Rosenau and Anderson<sup>5</sup> have shown that in spite of the enormous hypersensitivity acquired by guinea pigs following injection of minimal amounts of horse serum, immunizing processes were found to be simultaneously associated therewith; if the injection, instead of being done but once, is repeated for ten days, the ten times injected animal does not succumb to the reinjections of horse serum in contrast to the singly injected animal.

The combination of immunity and hypersensitivity appears most evident from the experience with vaccination.<sup>6</sup> The individual previously vaccinated compared to one vaccinated for the first time appears hypersensitive, because he reacts more quickly to the infection and at the same time he is protected. The vaccination causes in him only a small local reaction. He is spared all general symptoms.

Similar conditions in syphilis have been revealed recently by Finger and Landsteiner.<sup>7</sup> The reinoculation with syphilis has a distinct effect in all stages. This effect presents itself faster than in the case of a first infection; in other words, the incubation period is shorter. In tertiary syphilis reinoculation may be followed immediately by a local erythema, a process which may be regarded as identical with the "immediate reaction" following repeated serum injections.

*Immunity and hypersensitivity, therefore, can be connected most intimately with one another.*

These terms are, however, contradictory. Their union is a forced one. The concept of immunity, of course, goes back to the time when hypersensitivity was yet unknown.

However, as F. Hamburger<sup>8</sup> says, the specific alteration which an animal suffers after an experimental disease almost as frequently consists of an increased sensitivity as it consists of an increased resistance.

We require a new general term which prejudices nothing, a term to designate the alteration which occurs in the organism when it comes in contact with any organic living or lifeless poison.

*The vaccinated individual reacts to the vaccine, the luetic to the virus of syphilis, the tuberculous to the tuberculin, the individual injected with serum reacts to the serum differently than an individual who has not yet been in contact with the respective agent; yet he is far from being not sensitive. All we can say about him is that his capacity to react has changed.*

For this general concept of the *changed capacity to react* I suggest the term *Allergy*. Allos designates the deviation from the original condition, from normal behavior, as in the words allorhythmia and allotropy. The

vaccinated, the tuberculous, the individual injected with serum become *allergic* with regard to the respective foreign bodies. A foreign body, in turn, which conditions the organism to a change of reactivity as a result of one or more incorporations is to be called an *allergen*. The term is formed as an analogy (in an, of course, not philological manner) to the term antigen (Detre-Deutsch). This latter term designates a substance which is capable to produce antibodies. The concept of allergen is more far reaching. It includes in addition to the antigens numerous protein bodies which do not produce antibodies but cause hypersensitivity. Everything which causes diseases followed by immunity is to be regarded as an allergen. There are also to be included in this category the poisons of mosquitoes and bees insofar as they are followed by signs of hypo- or hyper-sensitivity. For this reason we have to include in this category the pollens of the hay fever (Wolff-Eisner), the urticaria producing substances of the strawberries and crabs and probably also a series of organic substances which lead to idiosyncrasy.

*The term immunity should be restricted to those processes in which the incorporation of the foreign substance does not produce any clinical reaction, where, therefore, complete insensitivity is present.* It makes no difference whether this be caused by alexins (natural immunity), by antitoxins (active and passive immunity against diphtheria or tetanus), or by a sort of adaptation to the poison (Wassermann and Citron).

The new terms do not interfere with the present nomenclature. The sharply defined concepts of antitoxin, cytolyisin, hemolysin, precipitin, agglutinin, coagulin are not disturbed thereby. Hypersensitivity is a new field of research in which only during the last few years the formation of the concepts occurred by a painful adaptation to the old terms.

In order to bring clarity into the development of these concepts, I suggest these new designations. I hope that by this simplification of the external forms I shall facilitate the study of these interesting phenomena for new students in this field.

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## BRONCHIAL ASTHMA IN THE YOUNG MALE ADULT

### A Study of Fifty Patients Returned from the Tropics for Bronchial Asthma, as Compared to Fifty Asthmatics Stationed in the United States

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THE purpose of this study is to discover what differences in findings, if any, exist in a group of patients returned from tropical areas for asthma as compared to an equal number of perennial asthmatics who never left the borders of the United States.

These patients were admitted to the allergy ward of Wakeman General Hospital, Camp Atterbury, Indiana from August, 1944 to November, 1945. The group consisted entirely of enlisted men, with ages ranging between eighteen and thirty-nine.

That asthma has been a common cause of tropical medical casualties has been noted by many medical officers. Winkenwerder<sup>18</sup> reported that asthma represented 1.2 per cent of total admissions at a general hospital in the Southwest Pacific area. One typical evacuation order from that region returned twenty-four asthma patients to the United States out of a total of two hundred and twenty-nine medical casualties of all kinds.

The fifty patients in this study were all returned from the Southwest Pacific. They were evacuated either by ship or plane from New Guinea, Fiji, New Caledonia, New Hebrides, Hawaiian Islands, Solomon Islands and Northern Australia. Their tour of tropical duty ranged from three days to eighteen months, with an average for the group of about six months.

Army service in the home group varied from one week to five years, with a group average of about eighteen months.

#### INCIDENCE OF FIRST ASTHMA ATTACK

In the group returned from the tropics, twenty patients (40 per cent) had the first attack of asthma while in that area. In the U. S. group only seven (14 per cent) had their first attack of asthma after army induction. Almost three times as many soldiers in this series had their first attack of asthma in the tropics as compared with the incidence among those stationed in the United States. Leopold<sup>7</sup>, reporting on a group of soldiers from all overseas theatres, states 31.5 per cent developed the initial attack of asthma overseas.

In the group of tropical asthmas now being considered, it was not uncommon to find a soldier who had had no asthma for ten to fifteen

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## BRONCHIAL ASTHMA—ROSEN

TABLE I. X-RAY OF CHEST: POSITIVE FINDINGS

Fifty U. S. Asthmas		Fifty Tropical Asthmas	
Case Number		Case Number	
9	Moderate exaggeration broncho-vascular markings throughout.	45	Exaggeration broncho-vascular and hilar markings bilaterally, one week later normal.
92	Productive changes both lower lobes, result of previous lipiodol.	80	Accentuation of lung markings suggestive of pulmonary irritation.
94	Increased broncho-vascular markings.	93	Slight exaggeration broncho-vascular markings.
107	Productive changes both lower lobes, results of previous lipiodol.	123	Marked accentuation broncho-vascular markings, two weeks later normal.
112	Increased broncho-vascular markings.	132	Partial obscuration left costophrenic sinus, one week later normal.
129	Exaggeration broncho-vascular markings with some linear fibrotic changes at right first intercostal space.	125	Broncho-vascular markings exaggerated. Small calcified primary tuberculous complex right upper lobe.
134	Exaggerated broncho-vascular markings.	178	Moderate increase in broncho-vascular markings.
144	Exaggerated broncho-vascular markings.	150	Moderate increase in broncho-vascular markings. Three weeks later normal.
3	Slight central thickening and accentuation root branches toward left lower lobe.		

years, then had had severe attacks within days or weeks after arriving in New Guinea, whereas in the United States group it was rare to find such cases.

## BLOOD EOSINOPHILS

Three smears were taken on each patient at weekly intervals. In the home group the average of these three ranged from 1-12 per cent, with sixteen (32 per cent) having an average blood eosinophilia of 5 per cent or more. In the tropical group the average ranged from 0-15 per cent with 21 (42 per cent) having blood eosinophilia. All patients who had eosinophilia of 5 per cent or over received three stool examinations for ova and parasites. Both groups were entirely negative.

Tropical service *per se* did not seem to cause eosinophilia. A control group of fifty malaria and upper respiratory patients recently returned from the tropics had only two patients with an average eosinophil count over 5 per cent.

## X-RAY OF CHEST

All patients received an admission x-ray of the chest interpreted by the chief of the x-ray service. If findings were positive re-rays were taken at weekly intervals.

The slightly greater degree of eosinophilia encountered in the tropical group suggested the possibility that more positive chest x-rays might be present in this group, in the light of reports<sup>1,3,5</sup> in the literature of tropical eosinophilia with positive chest x-ray findings. However, there

## BRONCHIAL ASTHMA—ROSEN

was no essential difference in the chest x-rays of these two groups (see Table I). Forty-two of the tropical group had normal plates, as did forty-one of the United States group. There was no relationship between the eosinophilia and the chest x-ray findings.

TABLE II. SKIN TESTS (INTRACUTANEOUS)

	Fifty Tropical Asthmas	Fifty U. S. Asthmas
Dust (1-1000)	6	9
Timothy	21	13
Alternarius	5	3
Feathers	3	12
Orris	6	5
Dog Dander	2	4
Ragweed	19	16
Horse Dander	2	8
Silk	4	5
Glue	1	5
Hormodendrum	2	2
Cat Dander	1	2
Tobacco	2	3
Horse Serum	7	4
Pyrethrum	4	3
Wool	0	0
Kapok	3	0
Egg white	3	7
Milk	10	11
Beef	8	11
Wheat	2	2
Chicken	3	8
Tomato	3	4

## SKIN TESTS (INTRACUTANEOUS)

Lederle extracts in accepted dilutions were used in this series. Dust, tobacco and molds were obtained from Abbott Laboratories. A wheal of at least 0.5 to 1 cm. was necessary for a slight positive reaction, 1 to 2 cm. for a moderate reaction, 2 cm. for a marked reaction.

While the number of positive reactors in each of these groups is not large enough to draw positive conclusions, still the differences in some of the tests may be of enough significance to warrant further study (see Table II). For example, 42 per cent of tropical patients reacted to timothy, while only 26 per cent of the U. S. group did. Only 6 per cent of the tropical asthmas reacted to feathers, while 24 per cent of the U. S. group were positive. The latter group were in contact with feather pillows in the United States, whereas the overseas troops rarely enjoyed this luxury.

There were less positive reactions to the common foods in the tropical group, which may be explained by the fact that overseas troops usually subsist on canned, less allergenic foods.

It is common knowledge how rapidly everything becomes moldy in the tropics. This suggested the possibility that molds may be an important factor in the production of "tropical asthma." However, in this series the molds *Alternarius* and *Hormodendrum* produced disappointingly few positive reactions, though slightly higher in the tropical group. Perhaps the Southwest Pacific molds have an uninvestigated specificity.

## DISCUSSION

Why does asthma occur so much more frequently in American soldiers in the Southwest Pacific than among those in the United States? Text books on tropical medicine contain little or no allergic studies of these islands. In a recent text<sup>13</sup> bronchial asthma or "Guha" is described as endemic in Guam and the Micronesia Islands, especially common in changes of season (wet to dry and dry to wet). Inhalants suggested are coral and copra dust, rice and sugar cane pollen.

Tropical weather factors are certainly more extreme. Periods of rapid meteorologic changes are common in the tropics, with their well known adverse effects on asthma. Yogi<sup>20</sup> reports an increase in asthma among Japanese who emigrated from Japan to Formosa. He finds an increase of cases in the wet season. He concludes that acclimatization in the tropics has a certain connection with the genesis of bronchial asthma.

Perhaps grass pollen is one of the important causes. In this series there were 16 per cent more positive reactors to timothy in the tropical group than in the U. S. group. Forty-two per cent of the tropical group reacted to timothy as compared to 38 per cent who reacted to ragweed. In the U. S. group 26 per cent reacted to timothy and 32 per cent to ragweed (see Table II). Roddis<sup>10</sup> reports the most common pollen of Honolulu, Hawaii to be grasses (red top, Bermuda grass). Young<sup>21</sup> and his co-workers, discussing asthma in Hawaii, believe local dust which contains pollens of native grasses, weeds and trees to be the most exciting inhalant allergen. Sharwood<sup>11</sup> reports grasses as the most prevalent pollen in Australia.

The frequency and severity of tropical asthma in our soldiers must certainly have been influenced by physical and emotional strain both in and out of combat. In the tropics all troops, wherever possible, are given a week or so for acclimatization. Perhaps the allergic individual cannot acclimatize as well. Acid-base balance and water regulation may be disturbed.

Almost all overseas troops drank water containing a much higher percentage of chlorine than those at home. Watson and Kibler<sup>16</sup> reported a case of asthma due to the chlorine in drinking water.

Perhaps the intense sunlight in the tropics is a factor in the causation of asthma. Cruciani<sup>2</sup> reports solar irradiation as an allergen in an asthmatic patient.

Odors have been reported by Urbach<sup>14</sup> to act as allergenic agents. The tropics are redolent with scents of flowers and fruits.

Many of the South Pacific islands are noted for their insect population. Asthma caused by insect emanations has been reported as due to moths,<sup>15</sup> beetles<sup>12</sup>, water fleas<sup>17</sup>, weevils<sup>19</sup>, May fly<sup>4</sup> and mushroom fly.<sup>6</sup>

Wood smoke<sup>9</sup> has been reported as the cause of asthma. Certainly

## BRONCHIAL ASTHMA—ROSEN

the smoke, dust and chemical smoke screens of combat may be another factor in the multitudinous known and unknown causes of bronchial asthma.

Perhaps future investigations in the Southwest Pacific may lead to wider knowledge of this disease.

### SUMMARY

1. A group of fifty soldier patients returned from the tropics (Southwest Pacific) for bronchial asthma were studied at an army general hospital and compared to a group of fifty asthmatics who never left the United States.

2. In the group returned from the tropics 40 per cent had their first attack of asthma while in that area. In the U. S. group only 14 per cent had their first asthma after army induction.

3. In the tropical group 42 per cent had an average blood eosinophil count of 5 per cent or over, while in the U. S. group 32 per cent had eosinophilia. The control group of fifty malaria and upper respiratory patients recently returned from the tropics contained only 4 per cent with blood eosinophilia.

4. X-ray of the chest disclosed essentially no difference in findings between the two groups. Eighty-four per cent of the tropical group had normal plates, as did 82 per cent of the U. S. group. There was no relationship between the eosinophilia and chest x-ray findings.

5. Skin tests revealed 42 per cent of tropical patients reacted to timothy, as compared to 26 per cent of the U. S. group. Only 6 per cent of the tropical asthmas reacted to feathers, as compared to 24 per cent of the U. S. group. There were more positive reactors to the common foods in the U. S. group.

6. Possible explanations for the more frequent occurrence of asthma in the Southwest Pacific than in the United States are discussed.

### CONCLUSIONS

In American soldiers asthma occurs much more frequently in the Southwest Pacific than it does in the United States. Blood eosinophilia occurs more often in asthmatics returned from the tropics. There are no essential differences in chest x-ray findings. Skin tests show more reactors to grasses in the tropical group, whereas the U. S. group has more reactors to ragweed and common foods.

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## Allergic Causes of Pruritus Ani

(Continued from Page 378)

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## THE TREATMENT OF PENICILLIN URTICARIA WITH NICOTINIC ACID

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THE medical literature within the past two years has contained numerous articles relating to allergic reactions from the administration of penicillin. The early report of Lyons<sup>1</sup> indicated that reactions occurred to the use of penicillin in 5.7 per cent of army personnel under treatment with this drug for surgical infections. The subsequent release of penicillin for civilian use has confirmed the reports of the frequent occurrence of various allergic manifestations; and has presented the physician with a difficult problem for control.

During the past year, forty-one cases of allergic reactions to penicillin have come under my observation and seem worthy of recording from the standpoint of the method of treatment employed. These cases presented various types of manifestations, as well as varying degrees of reaction. Urticaria was the most common allergic response encountered. It occurred in thirty-seven of the total number of cases, either as the only allergic response, or in conjunction with other manifestations. Fifteen of the urticaria cases showed only a diffuse papular eruption over the body. This eruption remained largely discrete and without a marked tendency for the papules to coalesce into massive or giant wheals. The itching in these cases was intense and there was a burning or prickling sensation in the wheal. Twenty-two of the urticaria cases presented massive areas of whealing in which the itching was chiefly confined to the edges of the wheal, and the periods of intense itching seemed to come in waves. Angioneurotic edema of the face and particularly of the orbital areas occurred in twelve of these cases of urticaria, and there were two instances of angioneurotic edema of the genitalia. Three of the more severe cases of urticaria developed typical evidence of serum disease. The joints became swollen, stiff, and painful, the temperature was elevated, insomnia and exhaustion were present, and the urine showed the presence of albumen.

Three cases of contact dermatitis were observed. These occurred from the use of penicillin in the eyes. The lids became swollen and an eczematoid eruption was present with a flare over the malar areas, also moderate itching was present. One case of eczematoid dermatitis of the leg was encountered. This developed at the site of a varicose ulcer where penicillin had been employed in an ointment base.

### TREATMENT

When reactions to penicillin were first encountered, the attempts to alleviate the suffering and discomfort of the patients by the use of the commonly accepted drugs were not highly encouraging. Epinephrine,

ephedrine, intravenous calcium gluconate, vitamin K, morphine and finally benadryl were all tried, and while some degree of relief was obtained, it was usually several days before the condition subsided to the point of comfort for the patient.

In an attempt to secure prompt and lasting relief, intravenous nicotinic acid was used. In these forty-one cases, nicotinic acid in the amount of 35 milligrams in 8 to 10 cubic centimeters of distilled water was given intravenously. The injection is given into the cubital vein very slowly. When approximately 3 to 4 cubic centimeters of the solution have been injected, the patient will experience a flush. This will usually begin with a sensation of heat passing up the spine into the neck, face and scalp. Usually, a prickling sensation is present in the scalp and a general feeling of warmth over the entire body. A few will experience a feeling of swelling in the lips. The skin capillaries of the face, neck and arms dilate giving these areas a flushed appearance. This sensation will last only a few minutes. The injection is stopped during this period of the flush and the needle and syringe maintained in place in the cubital vein. When the flush begins to subside the injection may be continued. In most patients, the remainder of the solution may be injected without a recurrence of the flush sensations.

Within a few hours, the itching begins to subside; this is followed by a decrease in the urticaria and edema, and within twenty-four hours the patients are free of the greater part of their allergic manifestations to penicillin. In only four cases, has it been necessary to give a second injection the following day.

#### CONCLUSIONS

Intravenous nicotinic acid in doses of 35 milligrams in 10 c.c. of distilled water has proved most efficacious in relieving urticaria resulting from allergic reactions to penicillin.

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Thrombopenic purpura was produced experimentally in the dog by the injection of the heterophil antibody of the Forssman type present in the serum of the rabbit immunized against sheep erythrocytes. There resulted a direct injury to the blood vessels following intradermic, interaperitoneal and intra-arterial injections. Necrotic and hemorrhagic lesions occurred in the tissues supplied by the blood vessels following injections of this serum into arteries. The pancreas, liver, intestines and hind limb of the dog were studied during the observations.

# Department of Clinical Pathology and Laboratory Procedures

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## RAPID DARKFIELD TECHNIQUE FOR EXAMINING SPUTUM

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OCCASIONALLY, in the study of patients presenting chronic bronchitis with cough, productive sputum, and sometimes asthma, one encounters an individual presenting the findings of a chronic bronchial spirochetosis. Proper treatment of this condition will frequently relieve a large part of the symptoms. Such cases are seen often enough to warrant its consideration in the differential diagnosis of those patients presenting themselves for possible allergic respiratory disease.

The careful routine study of the sputa as a rule will reveal such a possibility. By far the most effective means of finding and identifying the spiral organisms which might be responsible for this condition is the darkfield examination. Unfortunately, this is an examination that is not done routinely. The reason for this, of course, is the difficulty of doing darkfield examinations simply and quickly. Although the modern apparatus available for this type of microscopy is far more efficient than the older type, nevertheless most of them require considerable time and care and the services of a well-trained technician to conduct them properly. There is available, however, a darkfield method of simplicity and speed which furnishes all of the information that is necessary in such a study. For a number of years we have used it in our laboratory, the simple darkfield element made by the Bausch and Lomb Optical Company which replaces the uppermost hemisphere of the Abbe condensing system. After we have examined the specimen by making a fresh mount of the sputum and viewing with the light field, the Abbe condenser is racked downward, the upper lense is replaced with the darkfield element, a large drop of water is placed on the top surface of the element, and the condenser is racked upward until contact is made between the slide and the drop of water. The blue glass daylight filter is removed from the usual microscopic lamp, the plain mirror of the microscope is utilized, and while viewing the field through the low power objective the Abbe condenser is adjusted to the proper level, the diaphragm being wide open, to illuminate the field most brightly. After this approximate focus is found, the four millimeter objective is turned into the field and refocusing and readjustment of the Abbe is done to bring out the

*(Continued on Page 403)*

# Editorial

*The opinions expressed by the writers of editorials in the ANNALS are individual and do not necessarily represent the group opinion of the Board or of the College.*

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## A BRIEF CRITIQUE OF THE NEWER ANTI-HISTAMINIC DRUGS

Now that we have passed through the first ragweed pollen season during which the anti-histaminic drugs have been available for fairly widespread distribution among a large group of hay fever sufferers, interesting conclusions can be drawn. The ragweed allergen can cause more trouble than practically any other allergen. Have the new drugs given satisfactory relief? Not to the extent observed in previous studies on *small groups of individuals*. It was these early investigations which permitted the manufacturers to release benadryl and pyribenzamine.

Scientific papers on these two drugs have appeared in medical journals and these papers have been exploited in the lay press. The latter publicity has given the general impression to laymen, as well as to uninformed physicians, that the drugs are a cure-all for most allergic diseases, of which now there are known to be over twenty distressing ones, some of which are disabling and affect in a major way 10 per cent or more of the populace. After a season's trial, and with the accumulated knowledge that these drugs produce in about one-fourth of the patients very annoying, and at times serious, symptoms including nausea, vomiting, headaches, disorientation, and drowsiness, there has arisen considerable confusion as to their merits and a basis for their use. The drugs were formulated and manufactured on the premise that the release of histamine is primarily the cause of the allergic reaction. Let us pause to reflect:

1. There are clinical manifestations similar to those produced by histamine in certain syndromes.
  - a. Giant hives and dermographism.
  - b. Cold hypersensitivity.
  - c. Light hypersensitivity.
  - d. Intradermal skin tests with allergens.
  - e. Shock after minute intradermal tests.
  - f. On the other hand, the positive patch test (allergic basis) is certainly not reproducible by histamine.
2. Abramson has summarized some experiments which are not compatible with the histamine theory.
  - a. Cross circulation experiments with animals and anaphylactic shock are essentially unsuccessful. This failure is in contrast with the experiment of Loewi with the acetylcholine heart.

## EDITORIAL

- b. There is no release of histamine or an equivalent H-substance when a sensitized uterus contracts in a suitable medium.
  - c. There is no evidence that a rapidly acting histaminase is present to decompose the histamine in isolated tissue experiments.
  - d. Increasing the tolerance of sensitized animals to histamine has not been unequivocally shown to decrease anaphylactic shock.
  - e. Certain drugs apparently augment the susceptibility of sensitized animals to the antigen but they have no similar action in histamine shock.
  - f. Histamine and anaphylactic shocks do not always produce similar changes in the agglutination of the blood in certain animals.
  - g. There is variation in the concentration of histamine in the blood in anaphylaxis in different animals. In certain animals there is an increase of histamine. In other animals there is a decrease.
  - h. The denervated iris is constricted during anaphylactic shock but is not constricted by histamine.
  - i. Injection of histaminase into animals does not affect their reactions to the injection of specific proteins nor does it protect guinea pigs against anaphylactic shock.
  - j. The quantitative relationship between allergen molecules injected and histamine liberated in sufficient quantity to produce shock is not available. Some novel type of chain reaction would be required.
  - k. The Arthus phenomenon is not reproduced by sizable doses of histamine.
  1. Many skin reactions could not be reproduced by histamine but by a fixed or high molecular weight substance.
3. The manufacturers of these drugs do not distinguish between the isolation of histamine as a chemical entity and the biological assay of unknown substances, which they call histamine, by their effects on isolated tissues.
4. In dermatitis, it should be stressed that positive reactions to the patch tests are not typically histamine reactions. Indeed, early in the history of the pharmacology of histamine, allergists introduced histamine day after day into the same site without producing patch test reactions. Abramson has shown that the skin may act as a reservoir for large quantities of histamine without producing irritation. Also the fact seems to be neglected that a whealing substance was never isolated by Lewis from the wheal or by Abramson from wheals of different types of reversed electrophoresis.
5. The work of Katz regarding the release of histamine after the sensitized skin reacts to ragweed pollen is certainly not convincing compared with the failure to isolate a whealing substance identifiable as histamine.

6. The published investigations of the manufacturers of one of these drugs would indicate that reagins are always present in the serum in urticaria. It is also definite that typical histamine symptoms are not always present. Certainly, there is no definite increase in the blood histamine in all cases of urticaria, as is implied in these publications.

7. It is mentioned that the investigative work done by the manufacturers of these drugs was done on animals and that ether was used as an anesthetic. It is well known that the use of ether reduces the probability of anaphylactic shock. Would one be justified in calling ether anti-histaminic? Again in this relation, epinephrine is called an anti-allergic substance. Why is epinephrine not called an anti-histaminic substance? Certainly, epinephrine causes vasoconstriction which is the opposite of vasodilation due to histamine.

Undoubtedly, these anti-histaminic drugs during their use relieve a certain percentage of hay fever patients and relieve the itching of eczema, or temporarily relieve hives, just as intravenous injections of histamine or epinephrine will do, which would indicate that the drugs may be beneficial to a certain group of patients, particularly to a limited number of seasonal hay fever cases. They do not offer any cure or hope of cure when used alone. Hay fever patients with mild symptoms have experienced a good result when taking the anti-histaminic drugs, but these patients are often relieved by sedatives, hot drinks, or rest. Some patients with a moderate amount of hay fever have done well but the results are not consistent. Some days the drugs have blocked symptoms, other days there has been no response. This has probably been due to the fact that there is a tendency to great fluctuation in the pollen counts. When they are high, more drug is necessary, and when they are low, less is necessary, but if the patient forgets to make this decrease in dosage, then side reactions are apt to occur. This feature alone makes use of the drug impracticable in some individuals.

Severe cases of hay fever benefit very little from the anti-histaminic drugs. Often there is a tendency to increase the dosage until levels twice those recommended are reached. These large amounts of benadryl and pyribenzamine are apt to cause side reactions in so many instances that a recent study, which will soon be published, reveals that four out of every five subjects had unpleasant results leading up to a discontinuance of the drugs.

The value of benadryl in asthma is even more to be questioned. This will be discussed in a subsequent editorial.

One of the most reliable, yet not completely fool-proof, methods of promising the patient some success from drug therapy, is the application of cutaneous tests. If wheal formation takes place, a good response to benadryl and pyribenzamine may occur, if side reactions are not

too bad. Erythematous reactions to the skin tests usually points to failure when the drugs are employed. Side reactions are not so apt to occur but if treatment is continued too long in hopes of obtaining ultimately some satisfactory relief, then there is always the danger in this latter group of subjects of causing a shift in the shock organ to the lungs with the development of a type of asthma which some observers have felt is rather difficult to handle. In chronic allergic conditions continued use of these drugs over a period of years is illogical.

Most cases of mild and moderate hay fever respond to specific immunization procedures with fairly good results; the more severe cases can offer a fairly large number of failures. The anti-histaminic drugs do not fill in the gap for they, too, do not promise too much for the severe sufferer. However, one ray of hope can be offered. Why not combine the two forms of therapy? Actually, this has taken place. Many of the individuals who are very sensitive to ragweed pollen are unable to receive a proper dosage schedule when the immunization method is carried out. Reactions following administration of the pollen extracts can be controlled with benadryl or pyribenzamine. Here the drugs are of distinct value.

It is too soon, however, to give the proper evaluation of these drugs until the period of over-enthusiasm has subsided and we can get more definite facts regarding the number who received unfavorable reactions or who developed new forms of allergy from the use of these drugs.

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## Darkroom Technique for Examining Sputum

*(Continued from Page 399)*

maximum brightness of particles in the field and the maximum darkness of the background. This can all be accomplished within thirty seconds or so, without the use of special slides or oil between the condenser and the slide or between the cover slip and the objective. No funnel stop is required within the objective. With very little practice one is able to bring out micro organisms with brilliance and of sufficient magnification that spiral organisms are readily demonstrated. This setup incidentally is of sufficient efficiency to reveal readily *Treponema pallida* in the examination for syphilis. As most of the spiral organisms involved in bronchial spirochetosis are much larger and coarser than the *Treponema* they are even more readily identified. In this manner we are able to complete a rapid darkfield survey of the sputum specimens at a cost of time of only two or three minutes beyond that to do a routine light field examination. On a number of occasions such an examination done routinely has revealed this condition when it was not suspected, and has given us a ready means of treatment as well as the avoidance of tedious and time-consuming therapeutic efforts pointed in other directions.

# News Items

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## ANNUAL MEETING

According to present plans, the annual meeting of the College will be held at Atlantic City just preceding the session of the American Medical Association. It will be a three-day session, Thursday, Friday, and Saturday, June 5, 6, and 7. Headquarters for the College will be at the Hotel Senator, and any overflow will be taken care of at the Hotel Seaside, a five-minute walk from the Senator. Reservations can be made through the office of the secretary-treasurer of the College for rooms for June 5, 6, and 7. Anyone wishing reservations to extend through the AMA meeting will have to make formal application through the AMA for reservations beyond that time. You will be sent a questionnaire by the AMA on which you will have to signify your first, second, and third choice of hotel. It will be necessary also to specify on this blank that you are attending the meeting of the American College of Allergists and the exact time you wish to have your room. You will then have no trouble securing reservations at the Senator or Seaside for the days of the AMA meeting if you follow this procedure. Please make your hotel reservations as early as possible this year.

The Program Committee is as follows:

Harold Abramson, M.D., *Chairman*, New York, N. Y.  
Rudolph Baer, M.D., New York, N. Y.  
Jerome Glaser, M.D., Rochester, N. Y.  
French K. Hansel, M.D., St. Louis, Mo.  
Mary H. Lovcless, M.D., New York, N. Y.  
Harry L. Rogers, M.D., New York, N. Y.

All pre-AMA meetings of related societies will terminate on June 8, before the AMA session.

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## ACA REPRESENTS INTERNATIONAL ASSOCIATION OF ALLERGISTS IN THE UNITED STATES

The Board of Regents of the American College of Allergists unanimously voted that the College become a member of the International Association of Allergists. It is fitting that the largest allergy society in the world should represent the United States in the rapidly developing International Association.

In the present age, it is inconceivable to continue to be nationalistic. In matters of science, erasing national lines will go far to eliminate the isolationism which impedes progress in any field.

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## NEW ALLERGY ROSTER

Dr. Jonathan Forman, 956 Bryden Road, Columbus 5, Ohio, Editor of the *Ohio State Medical Journal*, Director-General of the International Correspondence Club of Allergy, Third Vice President of The Friends of the Land, and Editor of *The Land Letter*, published by the Friends of the Land, is compiling a new directory of physicians interested in clinical allergy. This roster will include and indicate those who are Fellows and Associate Fellows in the College, those who are Fellows and Members in the Academy, members of other allergy societies in other countries, and those who are now preparing themselves to be allergy specialists as well as students of allergy.

This is an extremely valuable contribution and it is hoped that all who are interested will co-operate and forward to Doctor Forman the name and addresses of physicians who they think should be listed in the Directory.

Based upon the first Directory, which was published in 1942, we can expect an outstanding roster which will be of invaluable aid to all interested in allergy.

## NEWS ITEMS

### SPECIAL LISTING OF ACA MEMBERS IN THE AMERICAN MEDICAL DIRECTORY

We are pleased to report that membership in the American College of Allergists will be indicated in the next edition of the *American Medical Directory*.

A letter, dated July 18, 1946, was received from Mr. F. V. Cargill, Manager, Directory Department of the *American Medical Directory*, stating that in confirmation of our request the American Medical Association was pleased to advise that membership in the American College of Allergists will be included in the next edition of the *American Medical Directory*. The American Medical Association expects to begin compiling the new Directory in the near future.

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### INSTRUCTIONAL COURSE SET TO BREAK RECORDS

Registration for the Fall Graduate Instructional Course apparently is going to break all records. The course is to be conducted in the General Assembly Room of the Jefferson Medical College, 1025 Walnut Street, two short blocks from the Benjamin Franklin Hotel, at which most of the registrants will be housed. This assembly room will hold 600 people, has a loud speaker, and is adequate in every way.

Dr. Harry L. Rogers, head of the Department of Allergy of the Jefferson Medical College, will have charge of a local sub-committee for making local arrangements.

There are plenty of restaurants located near the school, and their names and addresses will be posted for the convenience of the registrants.

Please make your reservations through the office of the secretary-treasurer, stating the exact time of your arrival and departure from the hotel. It is almost impossible to secure any more single rooms at the Benjamin Franklin Hotel, but we may be able to secure some at neighboring hotels, if necessary. However, we will have plenty of twin-bed rooms which the hotel requires to be shared. We hope as many as possible will be willing to share the twin-bed rooms.

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### LIBRARY OF NEWSPAPER CLIPPINGS STARTED

The News and Press Release Section of the Division of Public Relations of the College, of which Dr. Albert V. Stoesser is chairman, is now starting to complete a library of clippings from lay publications concerning any and all subjects on allergy and allied conditions. It will be appreciated if members of the College and anybody else interested will please send these clippings, being sure to indicate where they appeared and the date. Frequently a patient will call the attention of the physician to an article on these subjects appearing in the lay press. We would appreciate it if you could obtain from your patients any such material which they might encounter. Please send the clippings to the office of the secretary-treasurer of the College. Photostatic copies will be made of these clippings and perforated for ready reference. Authoritative press releases will be made by the Associated Press, the United Press, and the International News Service, as well as by local newspapers. These news releases will be printed verbatim.

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### SOUTHWEST ALLERGY FORUM

The Southwest Allergy Forum will hold its annual meeting at Shreveport, Louisiana, on Monday, March 31 and Tuesday, April 1, 1947. The program which is now being arranged promises to be a very good one and will be published in a later issue of the *ANNALS*. Dr. W. H. Browning, of Shreveport, is president and Dr. Sim Hulsey, 505 Medical Arts Building, Fort Worth, Texas, is secretary. Dr. J. S. Shavin, Physicians and Surgeons Building, 803 Jordon, Shreveport, Louisiana, has charge of the hotel reservations. Based on previous programs, one can expect good papers and informal discussions on subjects of allergy.

## NEWS ITEMS

### SOUTHEASTERN ALLERGY ASSOCIATION

The second annual meeting of the Southeastern Allergy Association will be held January 18 and 19, 1947 at the Atlanta-Biltmore Hotel, Atlanta, Ga. Reservations should be made directly with the hotel. Association officers are Dr. Hal McCluney Davison, Atlanta, Ga., president; Dr. J. Warrick Thomas, Richmond, Va., vice president; and Dr. Katharine Baylis MacInnis, Columbia, S. C., secretary-treasurer.

### NATIONAL SOCIETY FOR MEDICAL RESEARCH

The National Society for Medical Research on September 5, 1946, made the following announcement:

Research on animals for the development of life-saving medical knowledge has been endorsed by the Chamber of Commerce of the United States in a statement of policy released recently by Howard Strong, Secretary of the Health Advisory Council of the Chamber of Commerce.

Mr. Strong announced the policy as the result of a referendum vote of member organizations. The statement submitted for the vote is as follows:

"In view of the great progress that has been made in preventive and curative medicine and surgery through animal research and the prospect of even greater progress in the future, the National Chamber is unalterably opposed to the prohibition of this scientific procedure. Such a prohibition would seriously hamper all medical progress."

Result of the vote was: 2,424 organizations in favor of the statement, 18 against. Represented in the poll were slightly over a million businessmen.

Mr. Strong, in a letter to Dr. A. J. Carlson, President of the National Society for Medical Research, announced the outcome of the Chamber of Commerce referendum and said, "We are therefore now in a position to present the chamber's opposition to any anti-vivisection legislation wherever such legislation rears its head, and when advisable and possible, a representative of the chamber can appear in opposition."

We are pleased to announce the return from service of the following members of the College and their present locations: Major Alexander R. Altose, 233 Cobb Building, Seattle 1, Washington; Captain Samuel S. Burden, 8145 Cadwalader Avenue, Elkins Park, Pennsylvania; Captain William H. Horwitz, 26 Gray Street, Cambridge 38, Massachusetts; Captain Benjamin Lieberman, 3051 N. Prospect Avenue, Milwaukee 11, Wisconsin; Lt. Sylvia Ruby, 60 Beals Street, Brookline, Massachusetts.

Dr. Hal McCluney Davison, Dr. C. Raymond Arp, and Dr. John S. Atwater announce their association for the practice of medicine at 207 Doctors Building, 478 Peachtree Street, Atlanta, Georgia. Their practice is limited to internal medicine and allergy.

Willard S. Small, M.D., announces the association of Catherine G. Pearson, M.D., at his new location, 136 North Madison Avenue, Pasadena 4, California. Their practice is limited to allergic diseases.

Owing to the illness of Dr. David M. Pipes, F.A.C.A., of Greensboro, North Carolina, who is incapacitated and hospitalized for an indefinite period, Mrs. Pipes is very desirous of finding a physician qualified to practice allergy who could

*(Continued on Page 408)*

# BOOK REVIEWS

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**TREATMENT OF BRONCHIAL ASTHMA.** Vincent J. Derbes, M.D., and Hugo T. Engelhardt, M.D. With chapters by a panel of contributors. 466 pages, 61 figures. Price \$8.00. Philadelphia, Pennsylvania: J. B. Lippincott Company, 1946.

There are nineteen eminent contributors to this handy sized volume which covers most adequately every aspect of the diagnosis and treatment of bronchial asthma and its complications. There are two parts consisting in all of twenty-three chapters.

Part I contains eight chapters of basic material dealing thoroughly with history, definition and classification, statistics, predisposing and contributing factors, anatomy and physiology of the respiratory tract, pathology, immunology and climatic and weather effects.

Part II contains fifteen chapters which give a most complete presentation of the intrinsic and extrinsic factors in bronchial asthma. Detailed chapters on the causes of troublesome asthmatic disorders such as house-dust, pollen, fungus spores, foods, bacteria, epidermal substances, parasitic agents, et cetera, are considered by authorities with sound judgment and wide experience.

This book, designed purposely for the general practitioner, is presented in a clear, detailed, systematic and well-arranged manner by a nationally known group of contributors qualified to present the various phases of asthma to which they were assigned. Nothing of value is omitted which will help the physician to diagnose as well as treat asthmatic disorders. Detailed consideration is given to desensitization, management of foci of infection, vaccine therapy, drugs and inhalation therapy. Specific, symptomatic and surgical treatment as well as avoidance measures are detailed. Of special interest is the question of life expectancy of the asthmatic and other actuarial considerations which are presented by an expert statistician.

The volume is unique in that it considers bronchial asthma from the point of view of the general practitioner, a very welcome innovation with the increasing number of books being published on the subject. The publishers are to be congratulated for the quality of paper, arrangement and excellent printing as well as illustrations. The book fills a need for the practicing physician who wants available workable information on how to diagnose and treat troublesome disorders seen in daily practice.

F. K. H.

**ASMA ALERGIA (ASTHMA ALLERGY).** Dr. Guido Ruiz-Moreno. 186 pages. Buenos Aires: Lopez & Etchegoyen, S.R.L., 1946.

The author devotes the first 139 pages to asthma and the remaining forty-seven pages to allergy. There are ten chapters on asthma, and four on allergy.

Chapter I deals with the definition of asthma. Chapter II is entirely devoted to the classification of asthma, namely, (a) symptomatic asthma, (b) allergic asthma, (c) essential asthma. Allergic asthma is subdivided into (1) pure allergic asthma, (2) bacterial allergic asthma, and (3) combined allergic asthma.

Chapter III embraces the pathological physiology of asthma. The author states that the stenosis, which occurs during the asthmatic attack or state, is due to the following causes which occur either separately or together: (a) congestion of the mucosa, (b) edema of the mucosa, (c) bronchospasm, (d) cellular infiltration of the mucosa, and (e) secretions accumulated in the bronchi.

Chapter IV deals with the symptomatology of asthma, as classified in Chapter II.

Chapter V comprises all the etiological factors of asthma in all its phases. As

## BOOK REVIEWS

specific causes, the author mentions all the inhalants or air-borne substances, like house-dust, pollens, animal danders, bacteria, et cetera. As non-specific causes he points to cold, heat, menstruation, puberty, menopause, endocrine disturbances, et cetera. He states that the causes of essential asthma are not known.

Chapter VI takes in all the methods of diagnosis of asthma in all its phases.

Chapter VII deals with the prognosis of asthma. He contends that the prognosis in symptomatic asthma is varied; that of pure allergic asthma is excellent. In bacterial transitory asthma, it is good. In bacterial allergic asthma due to bronchial infection, and when the condition is permanent, it is guarded. In allergic asthma with complication, it is good. In allergic combined asthma, it is guarded. He concludes the chapter by stating that the prognosis in essential asthma is not known.

Chapter VIII comprises forty pages. It is entirely devoted to the treatment of asthma, namely, eliminative, symptomatic and immunologic. The subject is excellently covered. Chapter IX covers all the complications and the sequela of asthma. Chapter X deals with the social problems of asthma. The author speaks of eugenesis, legislation, asthma in military service, prophylaxis (industrial), and professional re-education. He is strongly in favor of periodic medical examinations.

Chapter I of the second part deals with the definition and concept of allergy, hypersensitiveness, allergen, reagin, allergic state, allergic manifestation, and allergy and immunity.

Chapter II covers the classification of allergy, namely, anaphylaxis, atopy, non-reagenic familial allergy, contact dermatitis, drug allergy, infectious or bacterial allergy, and allergy due to heterologous proteins. Chapter III covers clinical allergy in general, namely, pathological physiology, etiology, symptomatology, diagnosis, prognosis, and treatment.

Chapter IV describes clinical allergy particularly. Under this topic he includes allergy of the upper respiratory tract, like vasomotor rhinitis, hay fever, head cold, spring coryza, et cetera. Allergic cough, allergic bronchitis, allergic eczema, allergic toxemia, other allergic syndromes, and heterologous serotherapy, are also included in this chapter.

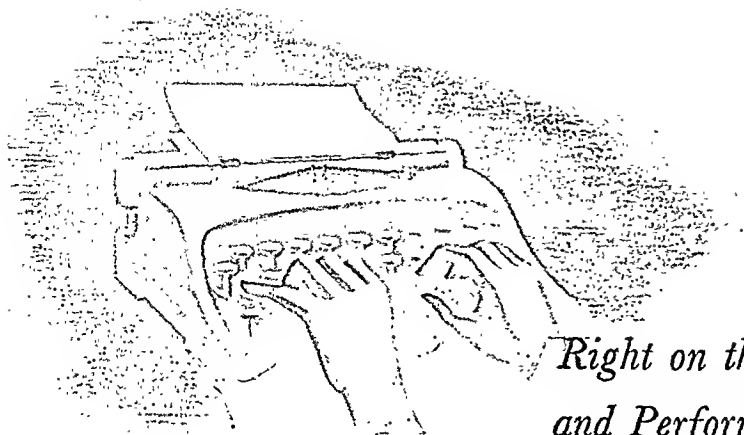
This book really contains a wealth of material, some new and some old. The author has succeeded in awakening new interests in this rapidly expanding field of allergy. This book would be of great interest to the allergist and to the general practitioner and medical student as well.

H. I. S.

## News Items

*(Continued from Page 406)*

come to Greensboro on a salary to handle the practice, perhaps with a view to the ultimate purchase. Doctor Pipes' clinic has a reserve group of new patients waiting for appointments, since he receives referred work from all sections of the state and various adjoining states. The office, the staff (technical, stenographic, and accounting), and the equipment are adequate to handle the present practice as well as the anticipated future increase. The accounting records are adequate and complete. Any allergist interested should contact Mrs. David M. Pipes, 217 Jefferson Building, Greensboro, North Carolina, directly.



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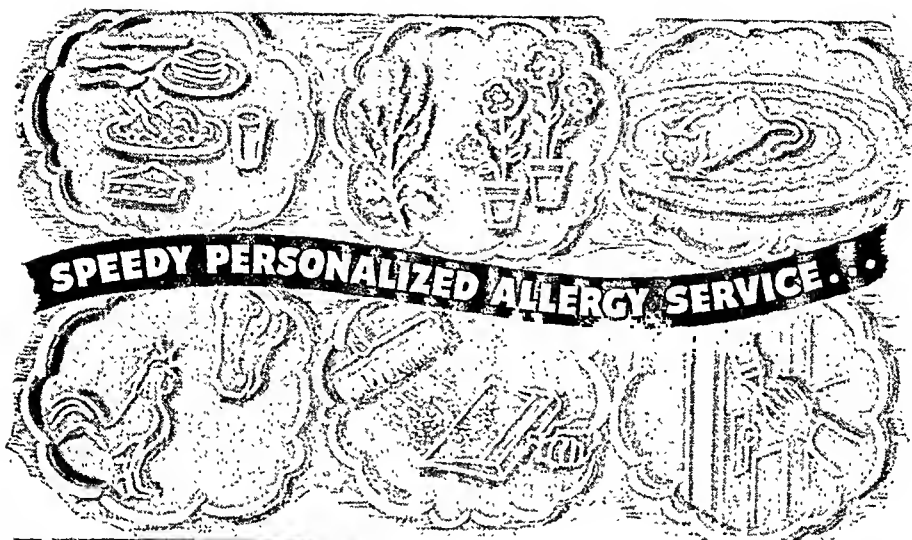
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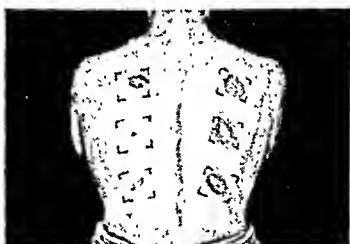
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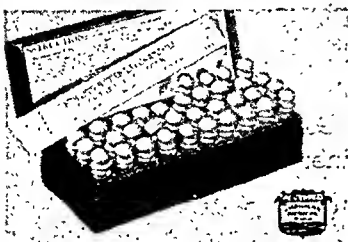
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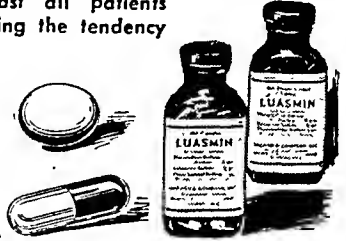
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the average woman would be lost without certain cosmetic aids to good grooming.

Certain cosmetic ingredients, notably orris root and rice starch, are more highly allergenic than others. It is a good practice for a cosmetic manufacturer not to use such ingredients because there is a relatively high incidence of hypersensitivity to them. Other ingredients, however, which seldom figure as allergens or irritants may nevertheless prove to be the allergic factor.

That is why we believe that when there is a history or suspicion of allergy, the subject should be tested with the cosmetic preparations she is using or contemplates using. If tests with the finished products are positive, further testing with their constituents is indicated to endeavor to determine the offending agents. These found, it is frequently possible for us to modify our formulas to exclude them.

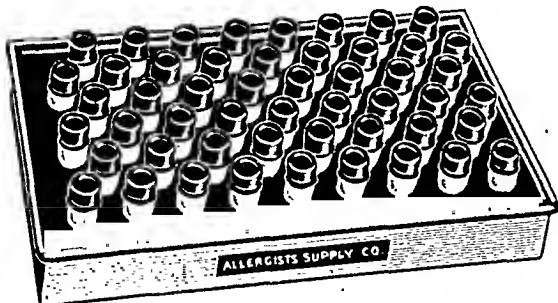
Luzier's Fine Cosmetics are selected to suit the individual's cosmetic requirements and preferences from a standpoint of whether her skin, viewed cosmetically, is normal, dry, or oily, and with regard to her coloring. We have a selection card for each of our patrons which roughly corresponds to a case history. Each of our selected products bears a label on which the patron's name and the registration number of the product are typed. Modified products bear a modification label, and a special modification card which carries a record of the patron's requirements is kept on file. We shall be pleased to send you our formulary, and in specific cases the raw materials for testing. We believe the patch test is best because it most closely approaches the conditions under which cosmetics are used.

**Luzier's, Inc., Makers of Fine Cosmetics & Perfumes**

KANSAS CITY, MO.

# SPECIALTIES FOR THE ALLERGIST

*Polished Stainless Steel Trays*



Holds forty-eight

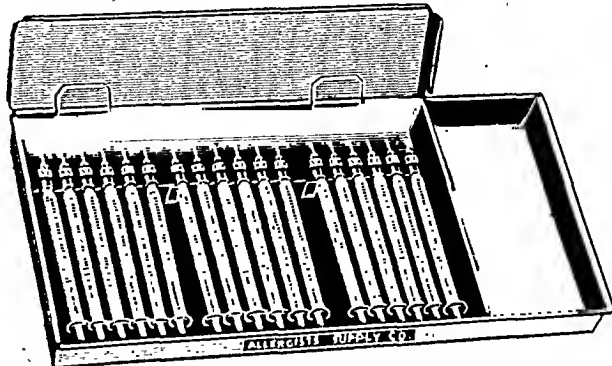
No. 16 Allergy Vials, 12 c.c., or

No. 8 Serum Vials, 10 c.c., or

No. 12 Army Vials, 10 c.c.

Size of Tray: 6"x13"x1½"

\$8.50 each



Holds eighteen Syringes; side compartment for used Syringes; flap cover protects the Needles.

Size of Tray 6"x13"x1"

\$6.50 each

QUANTITY DISCOUNT

*Other Stainless Steel Trays Made to Order.*

## ALLERGISTS SUPPLY CO.

458 Broadway, New York 13, N. Y.



*For Your Patients Who Are Sensitive to*

# BEDDING DUSTS

*you may safely prescribe*

## ALLERGEN-PROOF MATTRESS AND PILLOW ENCASINGS

If your diagnosis shows that a patient is sensitive to the offending dusts that are given off by cotton, wool, feathers, hair or kapok, you can do much to relieve the symptoms by instructing the patient to maintain a dust-free sleeping room.

In this remedial technique, you will

find it wise to prescribe Allergen-Proof Encasings for mattress and pillow. They are made of a special du Pont fabric which is dust-proof, soft and washable. They protect your patients from irritating substances in bedding materials, by confining the harmful allergens at their source.



SEND COUPON FOR FURTHER INFORMATION

**POST-WAR NEWS!**

Allergen-Proof Encasings are again available with Zippers

**ALLERGEN-PROOF ENCASINGS, INC.**

3 Park Place, New York 7, N. Y. or  
4046 Superior Ave., Cleveland 3, Ohio

Please send me without obligation:

- ☐ Patients' leaflets on avoidance of feathers and maintenance of a dust-free room.
- ☐ Sample of allergen-proof cloth.

\_\_\_\_\_  
\_\_\_\_\_  
\_\_\_\_\_  
City \_\_\_\_\_ State \_\_\_\_\_

## BY INJECTION



... subcutaneously or intramuscularly, ADRENALIN provides rapid symptomatic relief in asthmatic paroxysms; is useful in the prevention and treatment of other allergic reactions; localizes and prolongs the action of local anesthetics. Intravenously, it is used in shock and anesthetic accidents.

## BY APPLICATION



... for its vasoconstrictor action in hemorrhage, ADRENALIN permits better visualization of the field, and aids in the diagnosis and treatment of certain conditions encountered in ear, nose and throat practice.

## BY INSTILLATION



... into the nasal passage, ADRENALIN produces prompt decongestion; in the eye ADRENALIN decreases vascular congestion, and aids in the location of foreign bodies.

## BY INHALATION



... orally, ADRENALIN relieves severe attacks of bronchial asthma by relaxing the bronchial muscles.

Its remarkable ability to stimulate the heart and increase cardiac output, raise the blood pressure, constrict the peripheral arterioles, dilate blood vessels of voluntary muscles, and relax bronchial muscles... makes ADRENALIN one of the most versatile and useful therapeutic agents at the command of the physician. Little wonder, then, that it's

always kept close at hand in operating room, office, and medical bag.

To permit full use of its many therapeutic applications, there is a form of ADRENALIN (Epinephrine) to meet every medical need: Solutions of 1:100, 1:1000, 1:2600, 1:10,000; Suspension of 1:500 in oil; and Inhalant, Suppository, and Ointment.

# ADRENALIN

ORIGINAL

## PARKE, DAVIS & COMPANY

DETROIT 32 • MICHIGAN

# MEAD PRODUCTS

## of Interest to Allergists

### Nutramigen

1 lb. packages

A feeding for milk-sensitive infants, which contains a non-antigenic form of nitrogen (Amigen) as the protein component, combined with other food essentials.

### Sobee

1 and 4 lb. packages

A soybean food designed as a substitute for infants exhibiting idiosyncrasy to milk protein.

### Pabium

½ lb. and 1 lb.-2 oz. packages

A palatable mixed cereal food, precooked and dried (needs no further cooking). Furnishes not only high food energy value but also thiamine and riboflavin and calcium, phosphorus and iron.

### Pabena

8 oz. packages

A new form of Pabium, in which the only cereal grain is oatmeal. Has essentially the same nutritional advantages of Pabium, and all of its convenient and economical points.

### Mead's Dextri-Maltose with Yeast Extract and Iron

1 and 5 lb. tins

Supplies, in addition to the carbohydrate value of Dextri-Maltose, thiamine and riboflavin (vitamins B<sub>1</sub> and G), and iron.

### Mead's Oleum Percomorphum with Other Fish Liver Oils and Viosterol

10 and 50 c.c. bottles  
Bottles of 50 and 250 83-mg. capsules

A source of vitamins A and D in which not more than 50% of the vitamin D content is derived from viosterol. Consists of liver oils of percomorph fishes, viosterol, and fish liver oil. Each gram contains not less than 60,000 vitamin A units and 8,500 vitamin D units (U.S.P.).

### Mead's Cod Liver Oil Fortified with Percomorph Liver Oil

3 oz. and 16 oz. bottles

Consists of Mead's Standardized Cod Liver Oil with percomorph and other fish liver oils. Not less than 50% of the vitamin content is derived from percomorph liver oil. Supplies not less than 6,000 vitamin A units and 800 vitamin D units (U.S.P.) per gram.

### Mead's Standardized Cod Liver Oil

4 oz., 8 oz. and 16 oz. bottle

Each gram supplies not less than 1,800 vitamin A units and 175 vitamin D units (U.S.P.).

### Mead's Viosterol in Oil

10 c.c. and 50 c.c. bottles

For disturbances of calcium-phosphorus metabolism. Supplies 10,000 U.S.P. vitamin D units per gram.

### Mead's Cod Liver Oil with Viosterol

4 oz. and 16 oz. bottles

Contains 1,800 vitamin A units and 400 vitamin D units (U.S.P.) per gram.

### Mead's Viosterol in Halibut Liver Oil

10 c.c. and 50 c.c. bottles

Supplies 60,000 vitamin A units and 10,000 vitamin D units (U.S.P.) per gram.

### Mead's Halibut Liver Oil

10 c.c. and 50 c.c. bottles

For vitamin A therapy. Each gram supplies 60,000 vitamin A units and 850 vitamin D units (U.S.P.)

### Mead's Brewers Yeast Tablets

Bottles of 250 and 1,000 tablets

For deficiencies of vitamin B complex. Each tablet contains not less than 0.06 mg. thiamine, 0.02 mg. riboflavin and 0.15 mg. niacin.

### Mead's Brewers Yeast Powder

6 oz. bottles

The same product as Mead's Brewers Yeast Tablets but supplied in powder form for use in infant feeding formulas.

### Mead's Ascorbic Acid Tablets

Bottles of 50 and 250 tablets  
25 mg. and 100 mg. tablets

For prevention and treatment of scurvy. Each tablet supplies 25 mg. of ascorbic acid, the equivalent of 500 international units of vitamin C. Also supplied in 100 mg. tablets.

### Mead's Thiamine Hydrochloride Tablets

Bottles of 50 and 250 tablets  
1 mg. and 5 mg. tablets

The anti-neuritic factor for prevention and treatment of beriberi and other deficiencies of vitamin B<sub>1</sub>. Tablets containing 1 mg. thiamine supply 330 international units; 5 mg. tablets supply 1,650 international units of vitamin B<sub>1</sub>.

### Mead's Riboflavin Tablets

Bottles of 50 tablets  
1 mg. and 5 mg. tablets

Each tablet supplies 1 mg. of riboflavin (vitamin G). Also supplied in 5 mg. tablets.

### Mead's Niacin Tablets

Bottles of 50 tablets

For treatment of pellagra. Each tablet contains 25 mg. niacin.

**MEAD JOHNSON & CO., Evansville, Indiana, U. S. A.**

